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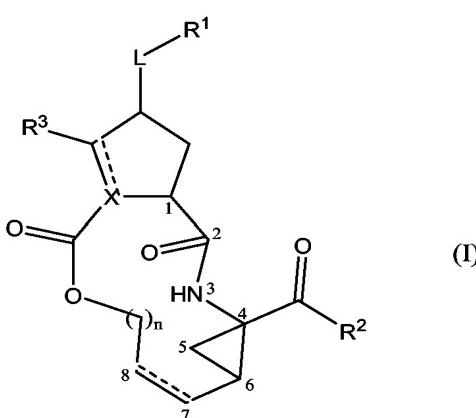
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(54) Title: MACROCYCLIC INHIBITORS OF HEPATITIS C VIRUS



(57) Abstract: Inhibitors of HCV replication of formula (I), the N-oxides, salts, and stereochemically isomeric forms thereof, wherein each dashed line (represented by -----) represents an optional double bond; X is N, CH and where X bears a double bond it is C; R¹ is aryl or a saturated, a partially unsaturated or completely unsaturated 5 or 6 membered monocyclic or 9 to 12 membered bicyclic heterocyclic ring system wherein said ring system contains one nitrogen, and optionally one to three additional heteroatoms selected from the group consisting of oxygen, sulfur and nitrogen, and wherein the remaining ring members are carbon atoms; wherein said ring system may be optionally substituted on any carbon or nitrogen ring atom with one, two, three, or four substituents; L is a direct bond, -O-, -O-C₁₋₄alkanediyl-, -O-C(=O)-, -O-C(=O)-NR^{4a}- or -O-C(=O)-NR^{4a}C₁₋₄alkanediyl-; R² is hydrogen, -OR⁵, -C(O)OR⁶, -C(=O)R⁶, -C(=O)NR^{4a}R⁶, -C(=O)NHR^{4c}, -NR⁵R³, -NHR^{4c}, -NR^{4a}SO_pNR^{4a}R³, -NR^{4a}SO_pR⁷, or B(OR⁷)₂; R³ is hydrogen, and where X is C or CH, R⁵ may also be C₁₋₆alkyl; n is 3, 4, 5, or 6; p is 1 or 2; aryl is phenyl, naphthyl, indanyl, or 1,2,3,4-tetrahydronaphthyl, each of which may be optionally substituted with one, two or three substituents; Het is a 5 or 6 membered saturated, partially unsaturated or completely unsaturated heterocyclic ring containing 1 to 4 heteroatoms each independently selected from nitrogen, oxygen and sulfur, being optionally condensed with a benzene ring, and wherein the group Het as a whole may be optionally substituted with one, two or three substituents; pharmaceutical compositions containing compounds (I) and processes for preparing compounds (I). Bioavailable combinations of the inhibitors of HCV of formula (I) with ritonavir are also provided.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

MACROCYCLIC INHIBITORS OF HEPATITIS C VIRUS

The present invention is concerned with macrocyclic compounds having inhibitory activity on the replication of the hepatitis C virus (HCV). It further concerns compositions comprising these compounds as active ingredients as well as processes for preparing these compounds and compositions.

Hepatitis C virus is the leading cause of chronic liver disease worldwide and has become a focus of considerable medical research. HCV is a member of the *Flaviviridae* family of viruses in the *hepacivirus* genus, and is closely related to the *flavivirus* genus, which includes a number of viruses implicated in human disease, such as dengue virus and yellow fever virus, and to the animal *pestivirus* family, which includes bovine viral diarrhea virus (BVDV). HCV is a positive-sense, single-stranded RNA virus, with a genome of around 9,600 bases. The genome comprises both 5' and 3' untranslated regions which adopt RNA secondary structures, and a central open reading frame that encodes a single polyprotein of around 3,010-3,030 amino acids. The polyprotein encodes ten gene products which are generated from the precursor polyprotein by an orchestrated series of co- and posttranslational endoproteolytic cleavages mediated by both host and viral proteases. The viral structural proteins include the core nucleocapsid protein, and two envelope glycoproteins E1 and E2. The non-structural (NS) proteins encode some essential viral enzymatic functions (helicase, polymerase, protease), as well as proteins of unknown function. Replication of the viral genome is mediated by an RNA-dependent RNA polymerase, encoded by non-structural protein 5b (NS5B). In addition to the polymerase, the viral helicase and protease functions, both encoded in the bifunctional NS3 protein, have been shown to be essential for replication of HCV RNA. In addition to the NS3 serine protease, HCV also encodes a metalloproteinase in the NS2 region.

Following the initial acute infection, a majority of infected individuals develop chronic hepatitis because HCV replicates preferentially in hepatocytes but is not directly cytopathic. In particular, the lack of a vigorous T-lymphocyte response and the high propensity of the virus to mutate appear to promote a high rate of chronic infection. Chronic hepatitis can progress to liver fibrosis leading to cirrhosis, end-stage liver disease, and HCC (hepatocellular carcinoma), making it the leading cause of liver transplantations.

There are 6 major HCV genotypes and more than 50 subtypes, which are differently distributed geographically. HCV type 1 is the predominant genotype in Europe and the US. The extensive genetic heterogeneity of HCV has important diagnostic and clinical

implications, perhaps explaining difficulties in vaccine development and the lack of response to therapy.

Transmission of HCV can occur through contact with contaminated blood or blood products, for example following blood transfusion or intravenous drug use. The introduction of diagnostic tests used in blood screening has led to a downward trend in post-transfusion HCV incidence. However, given the slow progression to the end-stage liver disease, the existing infections will continue to present a serious medical and economic burden for decades.

Current HCV therapies are based on (pegylated) interferon-alpha (IFN- α) in combination with ribavirin. This combination therapy yields a sustained virologic response in more than 40% of patients infected by genotype 1 viruses and about 80% of those infected by genotypes 2 and 3. Beside the limited efficacy on HCV type 1, this combination therapy has significant side effects and is poorly tolerated in many patients. Major side effects include influenza-like symptoms, hematologic abnormalities, and neuropsychiatric symptoms. Hence there is a need for more effective, convenient and better tolerated treatments.

Recently, two peptidomimetic HCV protease inhibitors have gained attention as clinical candidates, namely BILN-2061 disclosed in WO00/59929 and VX-950 disclosed in WO-03/87092. A number of similar HCV protease inhibitors have also been disclosed in the academic and patent literature. It has already become apparent that the sustained administration of BILN-2061 or VX-950 selects HCV mutants which are resistant to the respective drug, so called drug escape mutants. These drug escape mutants have characteristic mutations in the HCV protease genome, notably D168V, D168A and/or A156S. Accordingly, additional drugs with different resistance patterns are required to provide failing patients with treatment options, and combination therapy with multiple drugs is likely to be the norm in the future, even for first line treatment.

Experience with HIV drugs, and HIV protease inhibitors in particular, has further emphasized that sub-optimal pharmacokinetics and complex dosage regimes quickly result in inadvertent compliance failures. This in turn means that the 24 hour trough concentration (minimum plasma concentration) for the respective drugs in an HIV regime frequently falls below the IC₉₀ or ED₉₀ threshold for large parts of the day. It is considered that a 24 hour trough level of at least the IC₅₀, and more realistically, the IC₉₀ or ED₉₀, is essential to slow down the development of drug escape mutants. Achieving the necessary pharmacokinetics and drug metabolism to allow such trough levels provides a stringent challenge to drug design. The strong peptidomimetic nature

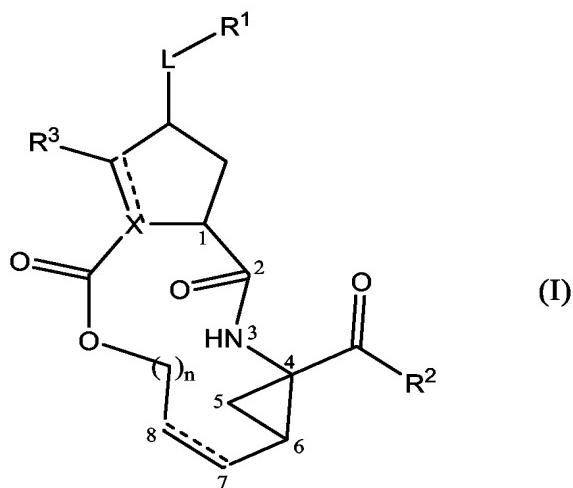
of prior art HCV protease inhibitors, with multiple peptide bonds poses pharmacokinetic hurdles to effective dosage regimes.

There is a need for HCV inhibitors which may overcome the disadvantages of current HCV therapy such as side effects, limited efficacy, the emerging of resistance, and compliance failures.

WO05/010029 discloses aza-peptide macrocyclic hepatitis C serine protease inhibitors; pharmaceutical compositions comprising the aforementioned compounds for administration to a subject suffering from HCV infection; and methods of treating an HCV infection in a subject by administering a pharmaceutical composition comprising the compounds of the present invention.

The present invention concerns inhibitors of HCV replication which are attractive not only in terms of their activity as HCV inhibitors but also for their good cell permeability and concomitant bioavailability.

The present invention concerns inhibitors of HCV replication, which can be represented by formula (I):



the *N*-oxides, salts, and stereochemically isomeric forms thereof, wherein each dashed line (represented by - - - -) represents an optional double bond; X is N, CH and where X bears a double bond it is C;

R¹ is aryl or a saturated, a partially unsaturated or completely unsaturated 5 or 6 membered monocyclic or 9 to 12 membered bicyclic heterocyclic ring system wherein said ring system contains one nitrogen, and optionally one to three additional heteroatoms selected from the group consisting of oxygen, sulfur and nitrogen, and wherein the remaining ring members are carbon atoms; wherein said

ring system may be optionally substituted on any carbon or nitrogen ring atom with one, two, three, or four substituents each independently selected from C₃₋₇cycloalkyl, aryl, Het, -C(=O)-NR^{4a}R^{4b}, -C(=O)R⁶, -C(=O)OR^{5a}, and C₁₋₆alkyl optionally substituted with C₃₋₇cycloalkyl, aryl, Het, -C(=O)NR^{4a}R^{4b}, -NR^{4a}R^{4b}, -C(=O)R⁶, -NR^{4a}C(=O)R⁶, -NR^{4a}SO_pR⁷, -SO_pR⁷, -SO_pNR^{4a}R^{4b}, -C(=O)OR⁵, or -NR^{4a}C(=O)OR^{5a}; and wherein the substituents on any carbon atom of the heterocyclic ring may also be selected from -OR⁸, -SR⁸, halo, polyhalo-C₁₋₆alkyl, oxo, thio, cyano, nitro, azido, -NR^{4a}R^{4b}, -NR^{4a}C(=O)R⁶, -NR^{4a}SO_pR⁷, -SO_pR⁷, -SO_pNR^{4a}R^{4b}, -C(=O)OH, and -NR^{4a}C(=O)OR^{5a};

L is a direct bond, -O-, -O-C₁₋₄alkanediyl-, -O-C(=O)-, -O-C(=O)-NR^{4a}- or -O-C(=O)-NR^{4a}C₁₋₄alkanediyl-;

R² represents hydrogen, -OR⁵, -C(=O)OR⁵, -C(=O)R⁶, -C(=O)NR^{4a}R^{4b}, -C(=O)NHR^{4c}, -NR^{4a}R^{4b}, -NHR^{4c}, -NR^{4a}SO_pNR^{4a}R^{4b}, -NR^{4a}SO_pR⁷, or B(OR⁵)₂;

R³ is hydrogen, and where **X** is C or CH, **R**³ may also be C₁₋₆alkyl;

n is 3, 4, 5, or 6;

p is 1 or 2;

each **R**^{4a} and **R**^{4b} are, independently, hydrogen, C₃₋₇cycloalkyl, aryl, Het, C₁₋₆alkyl optionally substituted with halo, C₁₋₄alkoxy, cyano, polyhaloC₁₋₄alkoxy, C₃₋₇cycloalkyl, aryl, or with Het; or **R**^{4a} and **R**^{4b} taken together with the nitrogen atom to which they are attached form pyrrolidinyl, piperidinyl, piperazinyl, 4-C₁₋₆alkylpiperazinyl, 4-C₁₋₆alkylcarbonyl-piperazinyl, and morpholinyl; wherein the morpholinyl and piperidinyl groups may be optionally substituted with one or with two C₁₋₆alkyl radicals;

R^{4c} is C₃₋₇cycloalkyl, aryl, Het, -O-C₃₋₇cycloalkyl, -O-aryl, -O-Het, C₁₋₆alkyl, or C₁₋₆alkoxy, wherein said C₁₋₆alkyl, or C₁₋₆alkoxy may be each optionally substituted with -C(=O)OR⁵, C₃₋₇cycloalkyl, aryl, or Het;

R⁵ is hydrogen; C₂₋₆alkenyl; Het; C₃₋₇cycloalkyl optionally substituted with C₁₋₆alkyl; or C₁₋₆alkyl optionally substituted with C₃₋₇cycloalkyl, aryl or Het;

R^{5a} is C₂₋₆alkenyl, C₃₋₇cycloalkyl, Het, or C₁₋₆alkyl optionally substituted with C₃₋₇cycloalkyl, aryl or Het;

R⁶ is hydrogen, C₁₋₆alkyl, C₃₋₇cycloalkyl, or aryl;

R⁷ is hydrogen; polyhaloC₁₋₆alkyl; aryl; Het; C₃₋₇cycloalkyl optionally substituted with C₁₋₆alkyl; or C₁₋₆alkyl optionally substituted with C₃₋₇cycloalkyl, aryl or Het;

aryl as a group or part of a group is phenyl, naphthyl, indanyl, or 1,2,3,4-tetrahydro-naphthyl, each of which may be optionally substituted with one, two or three substituents selected from halo, C₁₋₆alkyl, polyhaloC₁₋₆alkyl, hydroxy, C₁₋₆alkoxy, polyhaloC₁₋₆alkoxy, C₁₋₆alkoxyC₁₋₆alkyl, carboxyl, C₁₋₆alkylcarbonyl, C₁₋₆alkoxycarbonyl, cyano, nitro, amino, mono- or diC₁₋₆alkylamino, amino-

carbonyl, mono- or diC₁₋₆alkylaminocarbonyl, azido, mercapto, C₃₋₇cycloalkyl, phenyl, pyridyl, thiazolyl, pyrazolyl, pyrrolidinyl, piperidinyl, piperazinyl, 4-C₁₋₆alkylpiperazinyl, 4-C₁₋₆alkylcarbonyl-piperazinyl, and morpholinyl; wherein the morpholinyl and piperidinyl groups may be optionally substituted with one or with two C₁₋₆alkyl radicals; and the phenyl, pyridyl, thiazolyl, pyrazolyl groups may be optionally substituted with 1, 2 or 3 substituents each independently selected from C₁₋₆alkyl, C₁₋₆alkoxy, halo, amino, mono- or diC₁₋₆alkylamino;

Het as a group or part of a group is a 5 or 6 membered saturated, partially unsaturated or completely unsaturated heterocyclic ring containing 1 to 4 heteroatoms each independently selected from nitrogen, oxygen and sulfur, said heterocyclic ring being optionally condensed with a benzene ring, and wherein the group Het as a whole may be optionally substituted with one, two or three substituents each independently selected from the group consisting of halo, C₁₋₆alkyl, polyhalo-C₁₋₆alkyl, hydroxy, C₁₋₆alkoxy, polyhaloC₁₋₆alkoxy, C₁₋₆alkoxyC₁₋₆alkyl, carboxyl, C₁₋₆alkylcarbonyl, C₁₋₆alkoxycarbonyl, cyano, nitro, amino, mono- or diC₁₋₆alkyl-amino, aminocarbonyl, mono- or diC₁₋₆alkylaminocarbonyl, C₃₋₇cycloalkyl, phenyl, pyridyl, thiazolyl, pyrazolyl, pyrrolidinyl, piperidinyl, piperazinyl, 4-C₁₋₆alkylpiperazinyl, 4-C₁₋₆alkylcarbonyl-piperazinyl, and morpholinyl; wherein the morpholinyl and piperidinyl groups may be optionally substituted with one or with two C₁₋₆alkyl radicals; and the phenyl, pyridyl, thiazolyl, pyrazolyl groups may be optionally substituted with 1, 2 or 3 substituents each independently selected from C₁₋₆alkyl, C₁₋₆alkoxy, halo, amino, mono- or diC₁₋₆alkylamino.

The compounds of the present invention are surprising because despite their decreasing structural flexibility, they are active drugs against HCV. This is contrary to the currently prevailing opinion which expects less active drugs with less flexible macrocyclic rings.

The compounds of the present invention having relatively low molecular weight are easy to synthesize, starting from starting materials that are commercially available or readily available through art-known synthesis procedures.

The invention further relates to methods for the preparation of the compounds of formula (I), the N-oxides, addition salts, quaternary amines, metal complexes, and stereochemically isomeric forms thereof, their intermediates, and the use of the intermediates in the preparation of the compounds of formula (I).

The invention relates to the compounds of formula (I) *per se*, the N-oxides, addition salts, quaternary amines, metal complexes, and stereochemically isomeric forms

thereof, for use as a medicament. The invention further relates to pharmaceutical compositions comprising a carrier and an anti-virally effective amount of a compound of formula (I) as specified herein. The invention further relates to pharmaceutical compositions comprising the aforementioned compounds for administration to a subject suffering from HCV infection. The pharmaceutical compositions may comprise combinations of the aforementioned compounds with other anti-HCV agents.

The invention also relates to the use of a compound of formula (I), or a *N*-oxide, addition salt, quaternary amine, metal complex, or stereochemically isomeric forms thereof, for the manufacture of a medicament for inhibiting HCV replication. Or the invention relates to a method of inhibiting HCV replication in a warm-blooded animal said method comprising the administration of an effective amount of a compound of formula (I), or a *N*-oxide, addition salt, quaternary amine, metal complex, or stereochemically isomeric forms thereof.

As used in the foregoing and hereinafter, the following definitions apply unless otherwise noted.

The term halo is generic to fluoro, chloro, bromo and iodo.

The term “polyhaloC₁₋₆alkyl” as a group or part of a group, e.g. in polyhaloC₁₋₆alkoxy, is defined as mono- or polyhalo substituted C₁₋₆alkyl, in particular C₁₋₆alkyl substituted with up to one, two, three, four, five, six, or more halo atoms, such as methyl or ethyl with one or more fluoro atoms, for example, difluoromethyl, trifluoromethyl, trifluoroethyl. Preferred is trifluoromethyl. Also included are perfluoroC₁₋₆alkyl groups, which are C₁₋₆alkyl groups wherein all hydrogen atoms are replaced by fluoro atoms, e.g. pentafluoroethyl. In case more than one halogen atom is attached to an alkyl group within the definition of polyhaloC₁₋₆alkyl, the halogen atoms may be the same or different.

As used herein “C₁₋₄alkyl” as a group or part of a group defines straight or branched chain saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as for example methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2-methyl-1-propyl; “C₁₋₆alkyl” encompasses C₁₋₄alkyl radicals and the higher homologues thereof having 5 or 6 carbon atoms such as, for example, 1-pentyl, 2-pentyl, 3-pentyl, 1-hexyl, 2-hexyl, 2-methyl-1-butyl, 2-methyl-1-pentyl, 2-ethyl-1-butyl, 3-methyl-2-pentyl, and the like. Of interest amongst C₁₋₆alkyl is C₁₋₄alkyl.

The term “C₂₋₆alkenyl” as a group or part of a group defines straight and branched chained hydrocarbon radicals having saturated carbon-carbon bonds and at least one double bond, and having from 2 to 6 carbon atoms, such as, for example, ethenyl (or vinyl), 1-propenyl, 2-propenyl (or allyl), 1-butenyl, 2-butenyl, 3-butenyl, 2-methyl-2-propenyl, 2-pentenyl, 3-pentenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 2-methyl-2-butenyl, 2-methyl-2-pentenyl and the like. Of interest amongst C₂₋₆alkenyl is C₂₋₄alkenyl.

The term “C₂₋₆alkynyl” as a group or part of a group defines straight and branched chained hydrocarbon radicals having saturated carbon-carbon bonds and at least one triple bond, and having from 2 to 6 carbon atoms, such as, for example, ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 2-pentynyl, 3-pentynyl, 2-hexynyl, 3-hexynyl and the like. Of interest amongst C₂₋₆alkynyl is C₂₋₄alkynyl.

C₃₋₇cycloalkyl is generic to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. C₃₋₇cycloalkyl when substituted on aryl or Het in particular is cyclopropyl.

C₁₋₆alkanediyl defines bivalent straight and branched chain saturated hydrocarbon radicals having from 1 to 6 carbon atoms such as, for example, methylene, ethylene, 1,3-propanediyl, 1,4-butanediyl, 1,2-propanediyl, 2,3-butanediyl, 1,5-pentanediylyl, 1,6-hexanediylyl and the like. Of interest amongst C₁₋₆alkanediyl is C₁₋₄alkanediyl.

C₁₋₆alkoxy means C₁₋₆alkyloxy wherein C₁₋₆alkyl is as defined above.

As used herein before, the term (=O) or oxo forms a carbonyl moiety when attached to a carbon atom, a sulfoxide moiety when attached to a sulfur atom and a sulfonyl moiety when two of said terms are attached to a sulfur atom. Whenever a ring or ring system is substituted with an oxo group, the carbon atom to which the oxo is linked is a saturated carbon.

The bivalent radical L can be -O-C₁₋₄alkanediyl-, -O-CO-, -O-C(=O)-NR^{5a}- or -O-C(=O)-NR^{5a}-C₁₋₄alkanediyl-; these bivalent radicals in particular are linked to the pyrrolidine moiety by their oxygen atom.

The radical Het is a heterocycle as specified in this specification and claims. Examples of Het comprise, for example, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazinolyl, isothiazinolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl (including 1,2,3-triazolyl, 1,2,4-triazolyl), tetrazolyl, furanyl, thienyl, pyridyl, pyrimidyl, pyridazinyl, pyrazolyl-triazinyl, or any of such heterocycles condensed with a benzene ring, such as indolyl,

indazolyl (in particular 1*H*-indazolyl), indolinyl, quinolinyl, tetrahydroquinolinyl (in particular 1,2,3,4-tetrahydroquinolinyl), isoquinolinyl, tetrahydroisoquinolinyl (in particular 1,2,3,4-tetrahydroisoquinolinyl), quinazolinyl, quinoxaliny, cinnolinyl, phthalazinyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazinolyl, benzisothiazinolyl, benzothiazolyl, benzoxadiazolyl, benzothiadiazolyl, benzo-1,2,3-triazolyl, benzo-1,2,4-triazolyl, benzotetrazolyl, benzofuranyl, benzothienyl, benzopyrazolyl, and the like. Of interest amongst the Het radicals are those which are non-saturated, in particular those having an aromatic character. Of further interest are those Het radicals which are monocyclic.

Each of the Het or R¹ radicals mentioned in the previous and the following paragraph may be optionally substituted with the number and kind of substituents mentioned in the definitions of the compounds of formula (I) or any of the subgroups of compounds of formula (I). Some of the Het or R¹ radicals mentioned in this and the following paragraph may be substituted with one, two or three hydroxy substituents. Such hydroxy substituted rings may occur as their tautomeric forms bearing keto groups. For example a 3-hydroxypyridazine moiety can occur in its tautomeric form 2*H*-pyridazin-3-one. Some examples keto-substituted Het or R¹ radicals are 1,3-dihydro-benzimidazol-2-one, 1,3-dihydro-indol-2-one, 1*H*-indole-2,3-dione, 1*H*-benzo[*d*]isoxazole, 1*H*-benzo[*d*]isothiazole, 1*H*-quinolin-2-one, 1*H*-quinolin-4-one, 1*H*-quinazolin-4-one, 9*H*-carbazole, and 1*H*-quinazolin-2-one. Where Het is piperazinyl, it preferably is substituted in its 4-position by a substituent linked to the 4-nitrogen with a carbon atom, e.g. 4-C₁₋₆alkyl, 4-polyhaloC₁₋₆alkyl, C₁₋₆alkoxy-C₁₋₆alkyl, C₁₋₆alkylcarbonyl, C₃₋₇cycloalkyl.

R¹ can be a saturated, a partially unsaturated or completely unsaturated 5 or 6 membered monocyclic or 9 to 12 membered bicyclic heterocyclic ring system as specified in this specification and claims. Examples of said monocyclic or bicyclic ring system comprise for example, any of the rings mentioned in the previous paragraph as examples of the radical Het and additionally any of the monocyclic heterocycles mentioned in the previous paragraph condensed with pyridyl or pyrimidinyl such as, for example, pyrrolopyridine (in particular 1*H*-pyrrolo[2,3-*b*]pyridine, 1*H*-pyrrolo[2, 3-*c*]-pyridine), naphthyridine (in particular 1,8-naphthyridine), imidazopyridine (in particular 1*H*-imidazo[4, 5-*c*]pyridine, 1*H*-imidazo[4,5-*b*]pyridine), pyridopyrimidine, purine (in particular 7*H*-purine) and the like.

Interesting Het or R¹ radicals comprise, for example pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl (including 1,2,3-triazolyl,

1,2,4-triazolyl), tetrazolyl, furanyl, thienyl, pyridyl, pyrimidyl, pyridazinyl, pyrazolyl, triazinyl, or any of such heterocycles condensed with a benzene ring, such as indolyl, indazolyl (in particular 1H-indazolyl), indolinyl, quinolinyl, tetrahydroquinolinyl (in particular 1,2,3,4-tetrahydroquinolinyl), isoquinolinyl, tetrahydroisoquinolinyl (in particular 1,2,3,4-tetrahydroisoquinolinyl), quinazolinyl, phthalazinyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzoxadiazolyl, benzothiadiazolyl, benzofuranyl, benzothienyl.

Where Het is pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, 4-substituted piperazinyl, these radicals preferably are linked via their nitrogen atom (i.e. 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, 1-piperazinyl, 4-substituted piperazin-1-yl).

Each “aryl” is as specified above and preferably is phenyl substituted with the substituents specified above. This applies equally to arylC₁₋₆alkyl, which in particular can be arylmethyl, e.g. benzyl.

It should be noted that the radical positions on any molecular moiety used in the definitions may be anywhere on such moiety as long as it is chemically stable.

Radicals used in the definitions of the variables include all possible isomers unless otherwise indicated. For instance pyridyl includes 2-pyridyl, 3-pyridyl and 4-pyridyl; pentyl includes 1-pentyl, 2-pentyl and 3-pentyl.

When any variable occurs more than one time in any constituent, each definition is independent.

Whenever used hereinafter, the term “compounds of formula (I)”, or “the present compounds” or similar terms, it is meant to include the compounds of formula (I), each and any of the subgroups thereof, their prodrugs, N-oxides, addition salts, quaternary amines, metal complexes, and stereochemically isomeric forms. One embodiment comprises the compounds of formula (I) or any subgroup of compounds of formula (I) specified herein, as well as the N-oxides, salts, as the possible stereoisomeric forms thereof. Another embodiment comprises the compounds of formula (I) or any subgroup of compounds of formula (I) specified herein, as well as the salts as the possible stereoisomeric forms thereof.

The compounds of formula (I) have several centers of chirality and exist as stereochemically isomeric forms. The term “stereochemically isomeric forms” as used

herein defines all the possible compounds made up of the same atoms bound by the same sequence of bonds but having different three-dimensional structures which are not interchangeable, which the compounds of formula (I) may possess.

With reference to the instances where (*R*) or (*S*) is used to designate the absolute configuration of a chiral atom within a substituent, the designation is done taking into consideration the whole compound and not the substituent in isolation.

Unless otherwise mentioned or indicated, the chemical designation of a compound encompasses the mixture of all possible stereochemically isomeric forms, which said compound may possess. Said mixture may contain all diastereomers and/or enantiomers of the basic molecular structure of said compound. All stereochemically isomeric forms of the compounds of the present invention both in pure form or mixed with each other are intended to be embraced within the scope of the present invention.

Pure stereoisomeric forms of the compounds and intermediates as mentioned herein are defined as isomers substantially free of other enantiomeric or diastereomeric forms of the same basic molecular structure of said compounds or intermediates. In particular, the term "stereoisomerically pure" concerns compounds or intermediates having a stereoisomeric excess of at least 80% (i.e. minimum 90% of one isomer and maximum 10% of the other possible isomers) up to a stereoisomeric excess of 100% (i.e. 100% of one isomer and none of the other), more in particular, compounds or intermediates having a stereoisomeric excess of 90% up to 100%, even more in particular having a stereoisomeric excess of 94% up to 100% and most in particular having a stereoisomeric excess of 97% up to 100%. The terms "enantiomerically pure" and "diastereomerically pure" should be understood in a similar way, but then having regard to the enantiomeric excess, and the diastereomeric excess, respectively, of the mixture in question.

Pure stereoisomeric forms of the compounds and intermediates of this invention may be obtained by the application of art-known procedures. For instance, enantiomers may be separated from each other by the selective crystallization of their diastereomeric salts with optically active acids or bases. Examples thereof are tartaric acid, dibenzoyltartaric acid, ditoluoyltartaric acid and camphosulfonic acid. Alternatively, enantiomers may be separated by chromatographic techniques using chiral stationary phases. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically. Preferably, if a specific stereoisomer is desired, said compound is synthesized by stereospecific methods of

preparation. These methods will advantageously employ enantiomerically pure starting materials.

The diastereomeric racemates of the compounds of formula (I) can be obtained separately by conventional methods. Appropriate physical separation methods that may advantageously be employed are, for example, selective crystallization and chromatography, e.g. column chromatography.

For some of the compounds of formula (I), their *N*-oxides, salts, solvates, quaternary amines, or metal complexes, and the intermediates used in the preparation thereof, the absolute stereochemical configuration was not experimentally determined. A person skilled in the art is able to determine the absolute configuration of such compounds using art-known methods such as, for example, X-ray diffraction.

The present invention is also intended to include all isotopes of atoms occurring on the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include tritium and deuterium. Isotopes of carbon include C-13 and C-14.

The term "prodrug" as used throughout this text means the pharmacologically acceptable derivatives such as esters, amides and phosphates, such that the resulting *in vivo* biotransformation product of the derivative is the active drug as defined in the compounds of formula (I). The reference by Goodman and Gilman (*The Pharmacological Basis of Therapeutics*, 8th ed, McGraw-Hill, Int. Ed. 1992, "Biotransformation of Drugs", p 13–15) describing prodrugs generally is hereby incorporated. Prodrugs preferably have excellent aqueous solubility, increased bioavailability and are readily metabolized into the active inhibitors *in vivo*. Prodrugs of a compound of the present invention may be prepared by modifying functional groups present in the compound in such a way that the modifications are cleaved, either by routine manipulation or *in vivo*, to the parent compound.

Preferred are pharmaceutically acceptable ester prodrugs that are hydrolysable *in vivo* and are derived from those compounds of formula (I) having a hydroxy or a carboxyl group. An *in vivo* hydrolysable ester is an ester, which is hydrolysed in the human or animal body to produce the parent acid or alcohol. Suitable pharmaceutically acceptable esters for carboxy include C₁-alkoxymethyl esters for example methoxy-methyl, C₁-alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, C₃₋₈cycloalkoxycarbonyloxyC₁₋₆alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters for example 5-methyl-1,3-dioxolen-

2-onylmethyl; and C₁₋₆alkoxycarbonyloxyethyl esters for example 1-methoxycarbonyloxyethyl which may be formed at any carboxy group in the compounds of this invention.

An *in vivo* hydrolysable ester of a compound of the formula (I) containing a hydroxy group includes inorganic esters such as phosphate esters and α-acyloxyalkyl ethers and related compounds which as a result of the *in vivo* hydrolysis of the ester breakdown to give the parent hydroxy group. Examples of α-acyloxyalkyl ethers include acetoxy-methoxy and 2,2-dimethylpropionyloxy-methoxy. A selection of *in vivo* hydrolysable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, alkoxy carbonyl (to give alkyl carbonate esters), dialkylcarbamoyl and N-(dialkylaminoethyl)-N-alkylcarbamoyl (to give carbamates), dialkylaminoacetyl and carboxyacetyl. Examples of substituents on benzoyl include morpholino and piperazino linked from a ring nitrogen atom via a methylene group to the 3- or 4-position of the benzoyl ring.

For therapeutic use, salts of the compounds of formula (I) are those wherein the counter-ion is pharmaceutically acceptable. However, salts of acids and bases which are non-pharmaceutically acceptable may also find use, for example, in the preparation or purification of a pharmaceutically acceptable compound. All salts, whether pharmaceutically acceptable or not are included within the ambit of the present invention.

The pharmaceutically acceptable acid and base addition salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic acid and base addition salt forms which the compounds of formula (I) are able to form. The pharmaceutically acceptable acid addition salts can conveniently be obtained by treating the base form with such appropriate acid. Appropriate acids comprise, for example, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid, sulfuric, nitric, phosphoric and the like acids; or organic acids such as, for example, acetic, propanoic, hydroxyacetic, lactic, pyruvic, oxalic (i.e. ethanedioic), malonic, succinic (i.e. butanedioic acid), maleic, fumaric, malic (i.e. hydroxybutanedioic acid), tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, *p*-toluenesulfonic, cyclamic, salicylic, *p*-aminosalicylic, pamoic and the like acids.

Conversely said salt forms can be converted by treatment with an appropriate base into the free base form.

The compounds of formula (I) containing an acidic proton may also be converted into their non-toxic metal or amine addition salt forms by treatment with appropriate organic and inorganic bases. Appropriate base salt forms comprise, for example, the ammonium salts, the alkali and earth alkaline metal salts, e.g. the lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g. the benzathine, *N*-methyl-D-glucamine, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like.

The term addition salt as used hereinabove also comprises the solvates which the compounds of formula (I) as well as the salts thereof, are able to form. Such solvates are for example hydrates, alcoholates and the like.

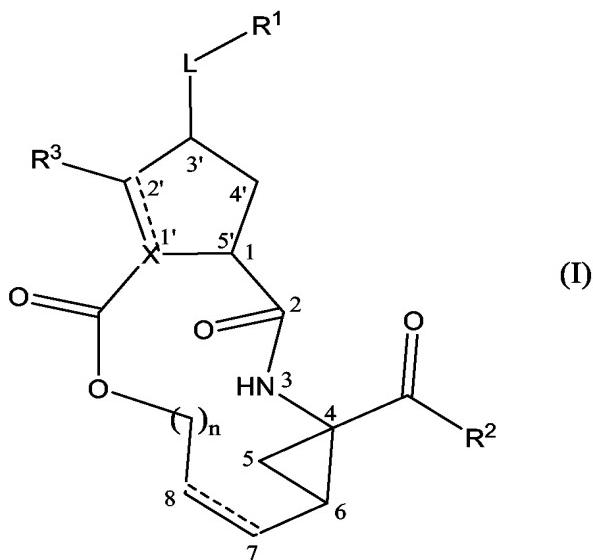
The term “quaternary amine” as used hereinbefore defines the quaternary ammonium salts which the compounds of formula (I) are able to form by reaction between a basic nitrogen of a compound of formula (I) and an appropriate quaternizing agent, such as, for example, an optionally substituted alkyl halide, aryl halide or arylalkyl halide, e.g. methyl iodide or benzyl iodide. Other reactants with good leaving groups may also be used, such as alkyl trifluoromethanesulfonates, alkyl methanesulfonates, and alkyl p-toluenesulfonates. A quaternary amine has a positive charged nitrogen. Pharmaceutically acceptable counterions include chloro, bromo, iodo, trifluoroacetate and acetate. The counterion of choice can be introduced using ion exchange resins.

The *N*-oxide forms of the present compounds are meant to comprise the compounds of formula (I) wherein one or several nitrogen atoms are oxidized to the so-called *N*-oxide.

It will be appreciated that the compounds of formula (I) may have metal binding, chelating, complex forming properties and therefore may exist as metal complexes or metal chelates. Such metalated derivatives of the compounds of formula (I) are intended to be included within the scope of the present invention.

Some of the compounds of formula (I) may also exist in their tautomeric form. Such forms although not explicitly indicated in the above formula are intended to be included within the scope of the present invention.

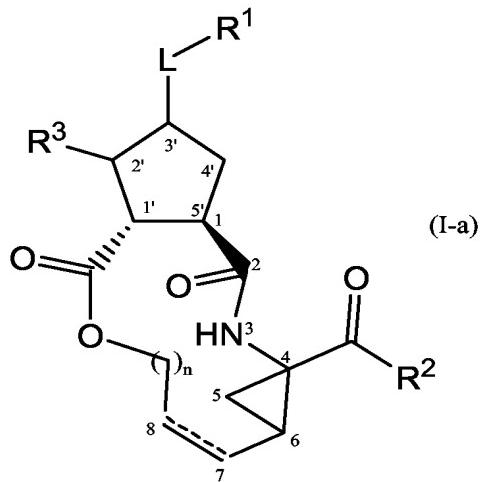
As mentioned above, the compounds of formula (I) have several asymmetric centers. In order to more efficiently refer to each of these asymmetric centers, the numbering system as indicated in the following structural formula will be used.



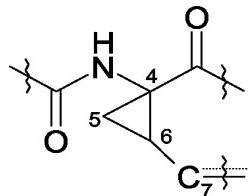
Asymmetric centers are present at positions 1, 4 and 6 of the macrocycle as well as at the carbon atom 3' in the 5-membered ring, carbon atom 2' when the R³ substituent is C₁₋₆alkyl, and at carbon atom 1' when X is CH. Each of these asymmetric centers can occur in their R or S configuration.

The stereochemistry at position 1 preferably corresponds to that of an L-amino acid configuration, i.e. that of L-proline.

When X is CH, the 2 carbonyl groups substituted at positions 1' and 5' of the cyclopentane ring preferably are in a trans configuration. The carbonyl substituent at position 5' preferably is in that configuration that corresponds to an L-proline configuration. The carbonyl groups substituted at positions 1' and 5' preferably are as depicted below in the structure of the following formula (I-a).

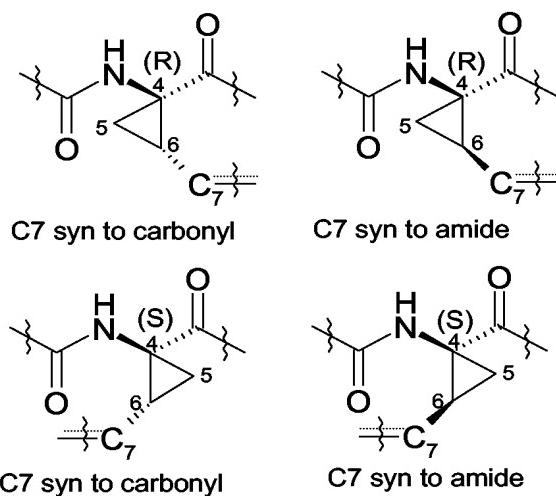


The compounds of formula (I) include a cyclopropyl group as represented in the structural fragment below:



wherein C₇ represents the carbon at position 7 and carbons at position 4 and 6 are asymmetric carbon atoms of the cyclopropane ring.

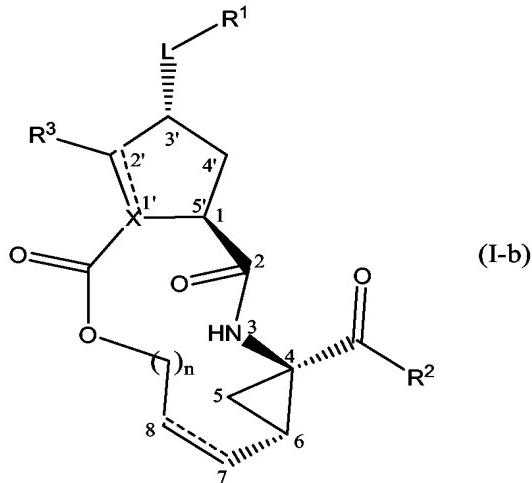
Notwithstanding other possible asymmetric centers at other segments of the compounds of formula(I), the presence of these two asymmetric centers means that the compounds can exist as mixtures of diastereomers, such as the diastereomers of compounds of formula (I) wherein the carbon at position 7 is configured either syn to the carbonyl or syn to the amide as shown below.



One embodiment concerns compounds of formula (I) wherein the carbon at position 7 is configured syn to the carbonyl. Another embodiment concerns compounds of formula (I) wherein the configuration at the carbon at position 4 is R. A specific subgroup of compounds of formula (I) are those wherein the carbon at position 7 is configured syn to the carbonyl and wherein the configuration at the carbon at position 4 is R.

The compounds of formula (I) may include a proline residue (when X is N) or a cyclopentyl or cyclopentenyl residue (when X is CH or C). Preferred are the compounds of formula (I) wherein the substituent at the 1 (or 5') position and the substituent -L-R¹ (at position 3') are in a trans configuration. Of particular interest are the compounds of formula (I) wherein position 1 has the configuration corresponding

to L-proline and the $-L-R^1$ substituent is in a trans configuration in respect of position 1. Preferably the compounds of formula (I) have the stereochemistry as indicated in the structure of formula (I-b) as depicted below:



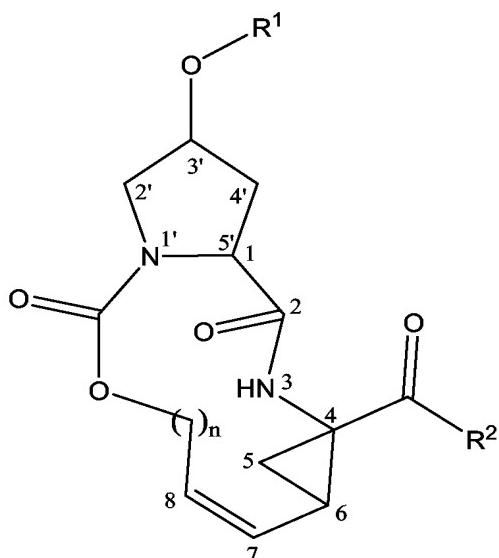
One embodiment of the present invention concerns compounds of formula (I) or of formulae (I-a), (I-b), or of any subgroup of compounds of formula (I), wherein one or more of the following conditions apply:

- (a) R^3 is hydrogen;
- (b) X is nitrogen;
- (c) L is $-O-$;
- (d) a double bond is present between carbon atoms 7 and 8.

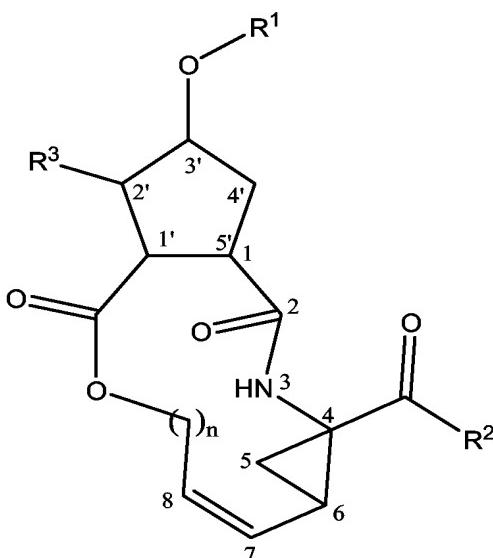
One embodiment of the present invention concerns compounds of formula (I) or of formulae (I-a), (I-b), or of any subgroup of compounds of formula (I), wherein one or more of the following conditions apply:

- (a) R^3 is hydrogen;
- (b) X is CH;
- (c) L is $-O-$;
- (d) a double bond is present between carbon atoms 7 and 8.

Particular subgroups of compounds of formula (I) are those represented by the following structural formulas:



(I-c)

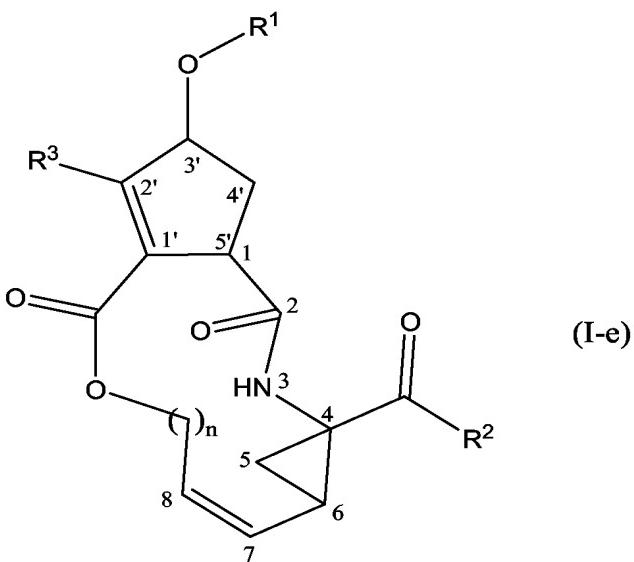


(I-d)

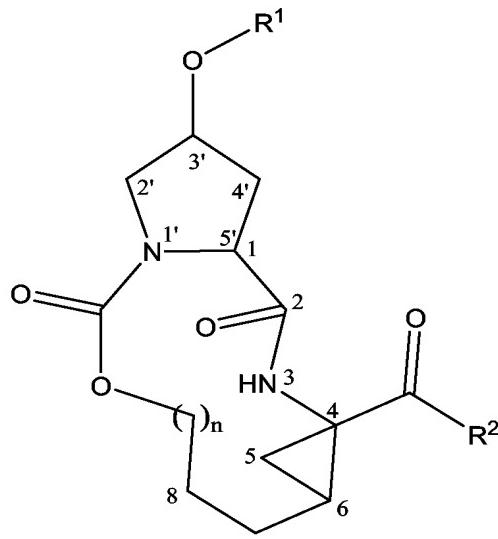
Amongst the compounds of formula (I-c) or (I-d), those having the stereochemical configuration of the compounds of formulae (I-a) and (I-b) are of particular interest.

The double bond between carbon atoms 7 and 8 in the compounds of formula (I), or in any subgroup of compounds of formula (I), may be in a *cis* or in a *trans* configuration. Preferably the double bond between carbon atoms 7 and 8 is in a *cis* configuration, as depicted in formulae (I-c) and (I-d).

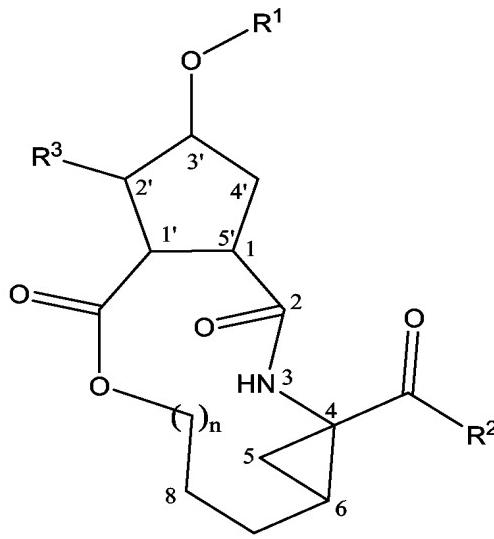
A double bond between carbon atoms 1' and 2' may be present in the compounds of formula (I), or in any subgroup of compounds of formula (I), as depicted in formula (I-e) below.



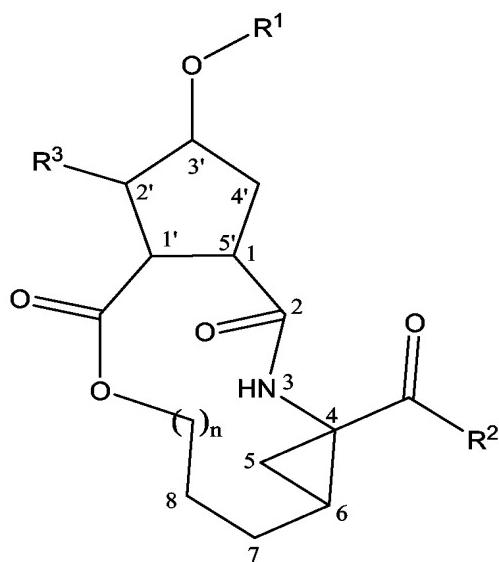
Yet another particular subgroup of compounds of formula (I) are those represented by the following structural formulae:



(I-f)



(I-g)



(I-h)

Amongst the compounds of formulae (I-f), (I-g) or (I-h), those having the stereochemical configuration of the compounds of formulae (I-a) and (I-b) are of particular interest.

In (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), (I-g) and (I-h), where applicable, L, X, n, R¹, R², and R³ are as specified in the definitions of the compounds of formula (I) or in any of the subgroups of compounds of formula (I) specified herein.

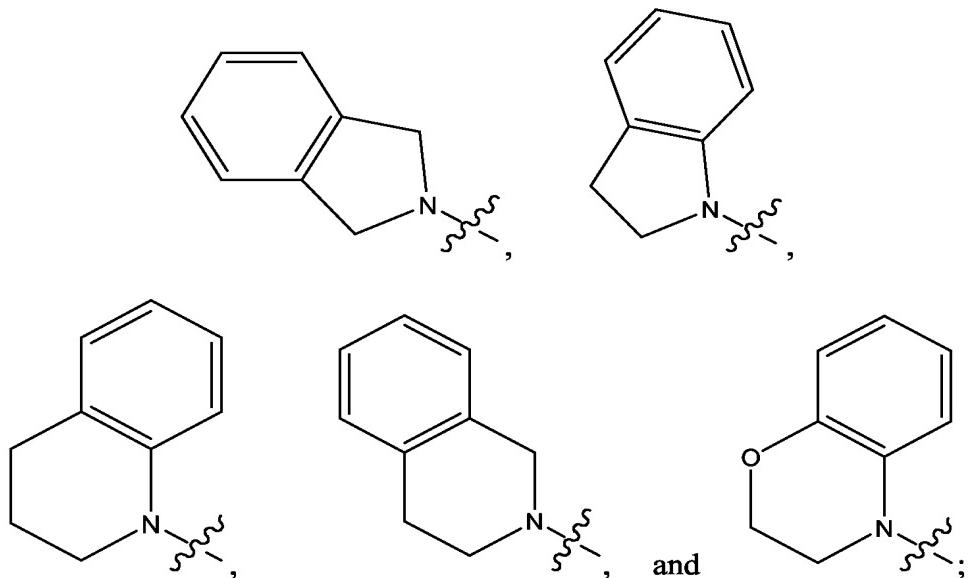
It is to be understood that the above defined subgroups of compounds of formulae (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), (I-g) or (I-h), as well as any other subgroup defined herein, are meant to also comprise any *N*-oxides, addition salts, quaternary amines, metal complexes and stereochemically isomeric forms of such compounds.

When n is 2, the moiety –CH₂- bracketed by “n” corresponds to ethanediyl in the compounds of formula (I) or in any subgroup of compounds of formula (I). When n is 3, the moiety –CH₂- bracketed by “n” corresponds to propanediyl in the compounds of formula (I) or in any subgroup of compounds of formula (I). When n is 4, the moiety –CH₂- bracketed by “n” corresponds to butanediyl in the compounds of formula (I) or in any subgroup of compounds of formula (I). When n is 5, the moiety –CH₂- bracketed by “n” corresponds to pentanediyl in the compounds of formula (I) or in any subgroup of compounds of formula (I). When n is 6, the moiety –CH₂- bracketed by “n” corresponds to hexanediyl in the compounds of formula (I) or in any subgroup of compounds of formula (I). Particular subgroups of the compounds of formula (I) are those compounds wherein n is 4 or 5.

Further subgroups of the compounds of formula (I) are those compounds of formula (I), or any subgroup of compounds of formula (I) specified herein, wherein R¹ is phenyl, naphthyl, pyridyl, pyridazinyl, triazolyl, tetrazolyl, quinolinyl, isoquinolinyl, quinazolinyl, pyrimidinyl, [1,8]naphthyridinyl, indolinyl, 1,2,3,4-tetrahydroquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl; all optionally substituted with one, two or three substituents selected from those mentioned in relation to R¹ in the definitions of the compounds of formula (I) or any of the subgroups of compounds of formula (I).

Other subgroups of the compounds of formula (I) are those compounds of formula (I), or any subgroup of compounds of formula (I) specified herein, wherein

- (a) R¹ is phenyl, naphthyl (such as naphth-1-yl, or naphth-2-yl), quinolinyl (in particular quinolin-4-yl), isoquinolinyl (in particular isoquinolin-1-yl), quinazolinyl (in particular quinazolin-4-yl), pyridyl (in particular 3-pyridyl), pyrimidinyl (in particular pyrimidin-4-yl), pyridazinyl (in particular pyridazin-3-yl and pyridazin-2-yl), [1,8]naphthyridinyl (in particular [1,8]naphthyridin-4-yl);
- (a) (b) R¹ is triazolyl (in particular triazol-1-yl, triazol-2-yl), tetrazolyl (in particular tetrazol-1-yl, tetrazol-2-yl), 6-oxo-pyridazin-1-yl, pyrazolyl (in particular pyrazol-1-yl), or imidazolyl (in particular imidazol-1-yl, imidazol-2-yl);
- (c) R¹ is a heterocycle selected from



and wherein each of the above mentioned R^1 radicals may be optionally substituted with one, two or three substituents selected from those mentioned in relation to R^1 in the definitions of the compounds of formula (I) or any of the subgroups of compounds of formula (I).

Embodiments of the invention are compounds of formula (I) or any of the subgroups of compounds of formula (I) wherein L is a direct bond, $-O-$, $-OC(=O)-$, or $-OC(=O)NR^{4a}-$, or in particular wherein L is $-OC(=O)NH-$ or $-O-$, or more in particular wherein L is $-O-$.

Preferably L is $-O-$, and R^1 is as specified above in (a). Preferably L is a direct bond, and R^1 is as specified above in (b). Preferably L is a bivalent radical $-OC(=O)-$, and R^1 is as specified above in (c).

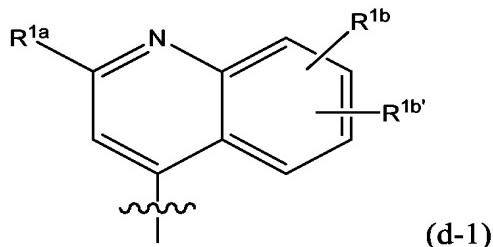
Embodiments of the invention are compounds of formula (I) or any of the subgroups of compounds of formula (I) wherein L is $-O-$ and R^1 is quinolinyl (in particular quinolin-4-yl), isoquinolinyl (in particular isoquinolin-1-yl), quinazolinyl (in particular quinazolin-4-yl), or pyrimidinyl (in particular pyrimidin-4-yl), either of which is, independently, optionally mono, di, or tri substituted with C_{1-6} alkyl, C_{1-6} alkoxy, nitro, hydroxy, halo, trifluoromethyl, $-NR^{4a}R^{4b}$, $-C(=O)NR^{4a}R^{4b}$, C_{3-7} cycloalkyl, aryl, Het, $-C(=O)OH$, or $-C(=O)OR^{5a}$; wherein aryl or Het are each, independently, optionally substituted with halo, C_{1-6} alkyl, C_{1-6} alkoxy, amino, mono- or di C_{1-6} alkylamino, pyrrolidinyl, piperidinyl, piperazinyl, 4- C_{1-6} alkylpiperazinyl (e.g. 4-methylpiperazinyl), thiomorpholinyl or morpholinyl; and wherein the morpholinyl, thiomorpholinyl and piperidinyl groups may optionally substituted with one or two C_{1-C_6} alkyl radicals.

Embodiments of the invention are compounds of formula (I) or any of the subgroups of compounds of formula (I) wherein L is $-O-$ and R¹ is quinolinyl (in particular quinolin-4-yl), isoquinolinyl (in particular isoquinolin-1-yl), quinazolinyl (in particular quinazolin-4-yl), or pyrimidinyl (in particular pyrimidin-4-yl), either of which is, independently, optionally mono, di, or tri substituted with methyl, ethyl, isopropyl, *tert*-butyl, methoxy, trifluoromethyl, trifluoromethoxy, fluoro, chloro, bromo, -NR^{4a}R^{4b}, -C(=O)NR^{4a}R^{4b}, phenyl, methoxyphenyl, cyanophenyl, halophenyl, pyridyl, C₁₋₄alkylpyridyl, pyrimidinyl, piperidinyl, morpholinyl, piperazinyl, C₁₋₄alkyl-piperazinyl, pyrrolidinyl, pyrazolyl, C₁₋₆alkyl-pyrazolyl, thiazolyl, C₁₋₆alkylthiazolyl, cyclopropylthiazolyl, or mono- or diC₁₋₆alkyl-aminothiazolyl; and wherein the morpholinyl, thiomorpholinyl and piperidinyl groups may optionally be substituted with one or two C_{1-C₆}alkyl (in particular one or two methyl) radicals.

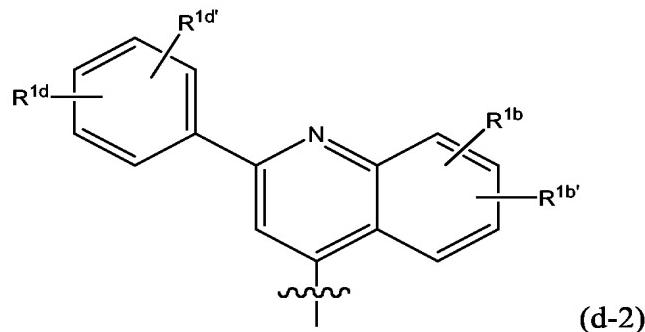
Embodiments of the invention are compounds of formula (I) or any of the subgroups of compounds of formula (I) wherein R¹ is quinolinyl, optionally substituted with 1, 2, 3 or 4 (or with 1, 2 or 3) substituents selected from those mentioned as possible substituents on the monocyclic or bicyclic ring systems of R¹, as specified in the definitions of the compounds of formula (I) or of any of the subgroups of compounds of formula (I).

Specific embodiments of the invention are those compounds of formula (I) or any of the subgroups of compounds of formula (I) wherein R¹ is

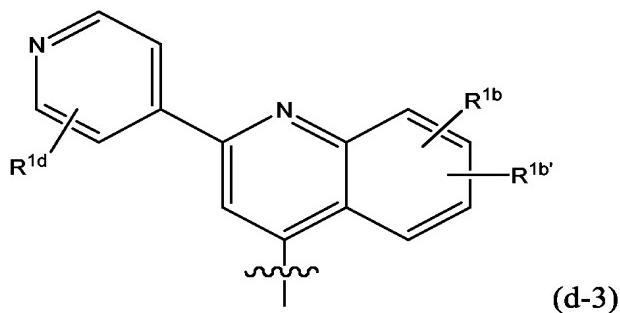
(d-1) a radical of formula



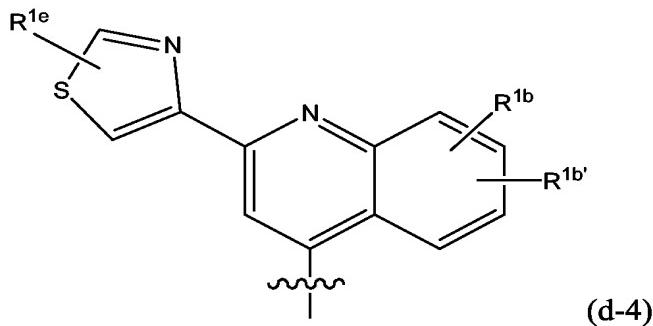
(d-2) a radical of formula



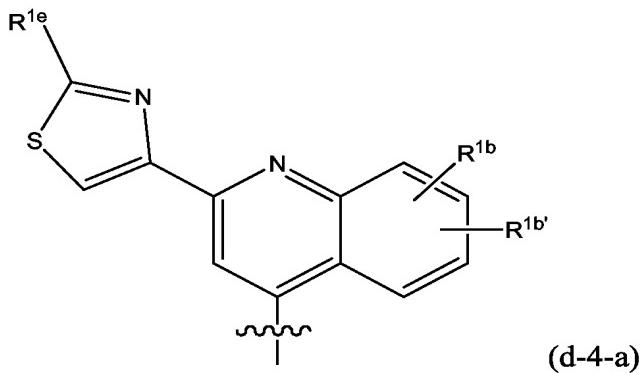
(d-3) a radical of formula



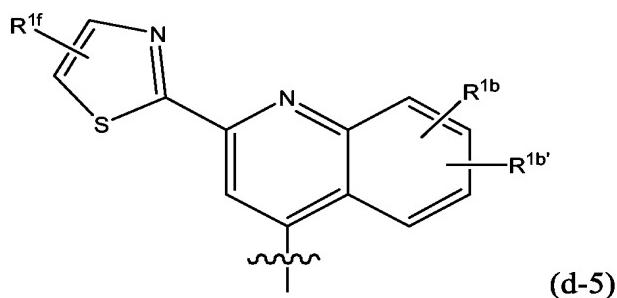
(d-4) a radical of formula



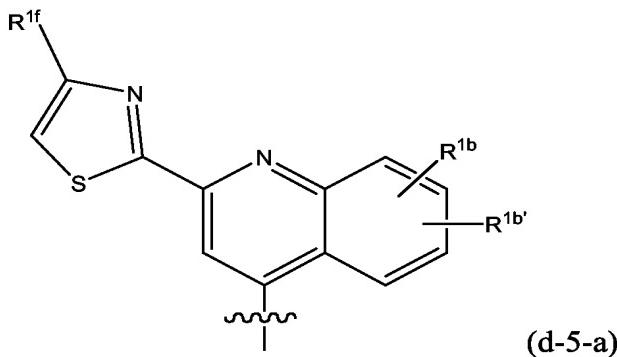
or in particular, (d-4-a) a radical of formula



(d-5) a radical of formula



or in particular, (d-5-a) a radical of formula



wherein in radicals (d-1) – (d-5), as well as in (d-4-a) and (d-5-a):

each R^{1a} , R^{1b} , $R^{1b'}$, R^{1d} , $R^{1d'}$, R^{1e} , R^{1f} are independently any of the substituents selected from those mentioned as possible substituents on the monocyclic or bicyclic ring systems of R^1 , as specified in the definitions of the compounds of formula (I) or of any of the subgroups of compounds of formula (I);

or, in particular, wherein in radicals (d-1) – (d-5), as well as in (d-4-a) and (d-5-a):

R^{1b} and $R^{1b'}$ may, independently, be hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, $-NR^{4a}R^{4b}$ (in particular amino or mono- or di C_{1-6} alkylamino), $-C(=O)NR^{4a}R^{4b}$, (in particular aminocarbonyl or mono- or di C_{1-6} alkylaminocarbonyl), nitro, hydroxy, halo, trifluoromethyl, $-C(=O)OH$, or $-C(=O)OR^{5a}$ (in particular wherein R^{5a} is C_{1-6} alkyl);

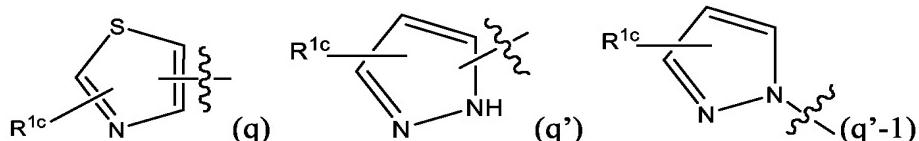
wherein each R^{4a} , R^{4b} , R^{5a} mentioned above or hereinafter independently is as defined in the definitions of the compounds of formula (I) or of any of the subgroups of compounds of formula (I);

or, in particular, wherein in radicals (d-1) – (d-5), as well as in (d-4-a) and (d-5-a):

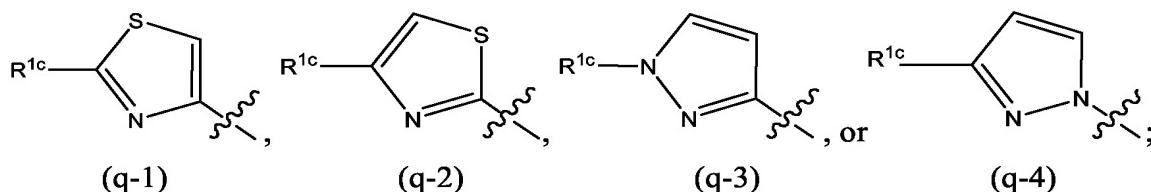
R^{1a} is hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, mono C_{1-6} alkylamino, amino, C_{3-7} cycloalkyl, aryl, or Het;

more specifically R^{1a} is C_{1-6} alkoxy, aryl or Het; of interest are embodiments wherein R^{1a} is methoxy, ethoxy, propoxy, phenyl, pyridyl, thiazolyl, pyrazolyl, each substituted as specified in the definitions of the compounds of formula (I) or of any of the subgroups of the compounds of formula (I); in specific embodiments said aryl or Het may each, independently, optionally substituted with C_{1-6} alkyl, C_{1-6} alkoxy, amino, mono- or di C_{1-6} alkylamino, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, 4- C_{1-6} alkylpiperazinyl; and wherein the morpholinyl, and piperidinyl groups may optionally substituted with one or two C_{1-6} alkyl radicals; and in particular R^{1a} can be a radical Het; wherein Het may include pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, 4- C_{1-6} alkylpiperazinyl; and wherein the morpholinyl, thiomorpholinyl and piperidinyl groups may optionally substituted with one or two C_{1-6} alkyl radicals;

Embodiments of the invention are compounds of formula (I) or any of the subgroups of compounds of formula (I) wherein R^{1a} is a radical



or, in particular, wherein R^{1a} is selected from the group consisting of:



wherein, where possible a nitrogen may bear an R^{1c} substituent or a link to the remainder of the molecule; each R^{1c} is any of the R^1 substituents may be selected from those mentioned as possible substituents on the monocyclic or bicyclic ring systems of R^1 , as specified in the definitions of the compounds of formula (I) or of any of the subgroups of compounds of formula (I);

specifically each R^{1c} may be hydrogen, halo, C₁₋₆alkyl, C₁₋₆alkoxy, polyhaloC₁₋₆alkyl (in particular trifluoromethyl), -NR^{4a}R^{4b} (in particular amino or mono- or diC₁₋₆alkyl-amino), -C(=O)NR^{4a}R^{4b}, (in particular aminocarbonyl or mono- or diC₁₋₆alkylamino-carbonyl), nitro, hydroxy, -C(=O)OH, or -C(=O)OR^{5a} (in particular wherein R^{5a} is C₁₋₆alkyl), phenyl, pyridyl, thiazolyl, pyrazolyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, 4-C₁₋₆alkylpiperazinyl (in particular 4-methylpiperazinyl); and wherein the morpholinyl and piperidinyl groups may optionally substituted with one or two C₁₋₆alkyl radicals;

more specifically each R^{1c} may be hydrogen, halo, C₁₋₆alkyl, amino, or mono- or di-C₁₋₆alkylamino, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, 4-C₁₋₆alkylpiperazinyl; and wherein the morpholinyl and piperidinyl groups may optionally substituted with one or two C₁₋₆alkyl radicals; and the phenyl, pyridyl, thiazolyl, pyrazolyl groups may be optionally substituted with 1, 2 or 3 (in particular with 1 or 2) substituents each independently selected from C₁₋₆alkyl, C₁₋₆alkoxy, halo, amino, mono- or diC₁₋₆alkylamino;

more specifically each R^{1c} may be hydrogen, halo, C₁₋₆alkyl, amino, or mono- or di-C₁₋₆alkylamino, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, 4-C₁₋₆alkylpiperazinyl; and wherein the morpholinyl and piperidinyl groups may optionally substituted with one or two C₁₋₆alkyl radicals;

and where R^{1c} is substituted on a nitrogen atom, it preferably is a carbon containing substituent that is connected to the nitrogen via a carbon atom or one of its carbon atoms;

specifically each R^{1d} and R^{1d'} independently may be hydrogen, C₁₋₆alkyl, C₁₋₆alkoxy, or halo;

or more specifically each R^{1d} in (d-3) may be hydrogen, C₁₋₆alkyl, C₁₋₆alkoxy or halo;

specifically R^{1e} may be hydrogen, C₁₋₆alkyl, amino, mono- or diC₁₋₆alkylamino, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, 4-C₁₋₆alkylpiperazinyl (in particular 4-methylpiperazinyl); and wherein the morpholinyl and piperidinyl groups may optionally substituted with one or two C₁₋₆alkyl radicals;

preferably each R^{1b} is C₁₋₆alkoxy, more preferably methoxy;

specifically R^{1f} may be hydrogen, C₁₋₆alkyl, amino, mono- or diC₁₋₆alkylamino, pyrrolidinyl, piperidinyl, piperazinyl, 4-C₁₋₆alkylpiperazinyl (in particular 4-methyl-piperazinyl), or morpholinyl.

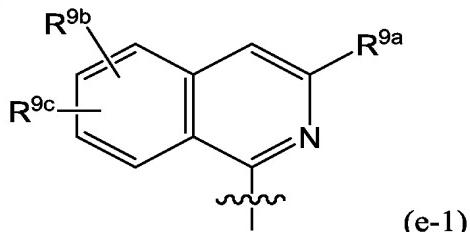
Specific embodiments of the invention are compounds of formula (I) or any of the subgroups of compounds of formula (I) wherein R¹ is 7-methoxy-2-phenyl-quinolin-4-yl and L is -O-.

Embodiments of the invention are compounds of formula (I) or any of the subgroups of compounds of formula (I) wherein R¹ is

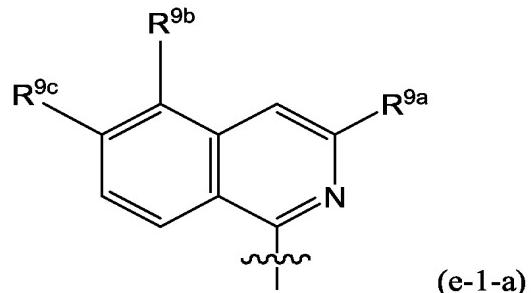
(e) isoquinolinyl (in particular 1-isoquinolinyl), optionally substituted with 1, 2, 3 or 4 (or with 1, 2 or 3) substituents selected from those mentioned as possible substituents on the monocyclic or bicyclic ring systems of R¹, as specified in the definitions of the compounds of formula (I) or of any of the subgroups of compounds of formula (I).

Specific such embodiments are those wherein R¹ is

(e-1) a radical of formula:



or in particular (e-1-a) a radical of formula:



wherein R^{9a}, R^{9b}, R^{9c} independently form one another are any of the substituents selected from those mentioned as possible substituents on the monocyclic or bicyclic ring systems of R¹, as specified in the definitions of the compounds of formula (I) or of any of the subgroups of compounds of formula (I); in particular

R^{9a} may have the same meanings as R^{1a} as specified above; in particular it may be aryl or Het, either of which is optionally substituted with any of the radicals mentioned as substituents of aryl or of Het as specified definitions of the compounds of formula (I) or of any of the subgroups of compounds of formula (I) (including the number of substituents); specifically said aryl or Het may be substituted with 1, 2 or 3 (in particular with one) radical or radicals R¹⁰; wherein said

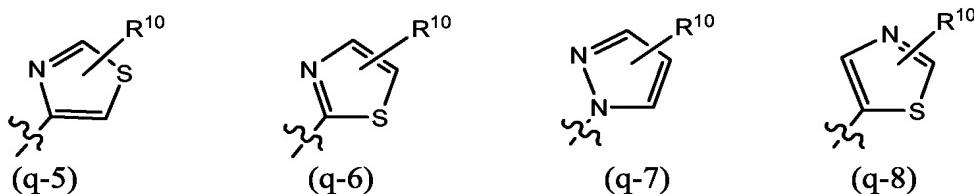
R¹⁰ is any of the radicals mentioned as substituents of aryl or Het as specified definitions of the compounds of formula (I) or of any of the subgroups of compounds of formula (I) as defined above; or in particular R¹⁰ is hydrogen, C₁₋₆alkyl, C₃₋₇cycloalkyl, phenyl, pyridyl, thiazolyl, pyrazolyl, amino optionally mono or disubstituted with C₁₋₆alkyl, or aminocarbonyl or mono- or diC₁₋₆alkylaminocarbonyl; wherein Het also includes pyrrolidinyl, piperidinyl, piperazinyl, 4-C₁₋₆alkylpiperazinyl (e.g. 4-methylpiperazinyl), or morpholinyl; and wherein the morpholinyl, or piperidinyl

groups may optionally be substituted with one or two C₁₋₆alkyl radicals; and the phenyl, pyridyl, thiazolyl, pyrazolyl groups may be optionally substituted with 1, 2 or 3 (in particular with 1 or 2) substituents each independently selected from C₁₋₆alkyl, C₁₋₆alkoxy, halo, amino, mono- or diC₁₋₆alkylamino;

R^{9b} may have the same meanings as R^{1b} as specified above; in particular it may be hydrogen, C₁₋₆alkyl, C₃₋₇cycloalkyl, aryl, Het, halo (e.g. bromo, chloro or fluoro); R^{9c} may have the same meanings as R^{1c} as specified above; in particular it may be is hydrogen or C₁₋₆alkoxy.

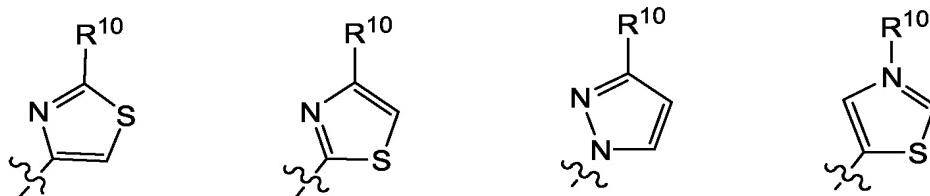
In particular R^{9a} in the isoquinolinyl radical specified under (e-1) or (1-e-a) includes phenyl, pyridyl, thiazolyl, oxazolyl or pyrazolyl either of which is optionally substituted with R¹⁰ as defined above, in particular optionally substituted with an R¹⁰ which may be hydrogen, C₁₋₆alkyl (e.g. methyl, ethyl, isopropyl, tert-butyl), amino, pyrrolidinyl, piperidinyl, piperazinyl, 4-C₁₋₆alkylpiperazinyl (e.g. 4-methylpiperazinyl), or morpholinyl, C₁₋₆alkylamino, (C₁₋₆alkyl)₂amino, aminocarbonyl, or mono- or diC₁₋₆alkylaminocarbonyl; and wherein the morpholinyl, and piperidinyl groups may optionally substituted with one or two C₁₋₆alkyl radicals.

Preferably R^{9a} in the isoquinolinyl radical specified under (e-1) or (e-1-a) includes any of radicals (q), (q'), (q'-1), (q-1), (q-2), (q-3), (q-4) specified above as well as:



wherein each R¹⁰ is any of the radicals mentioned as substituents of Het as specified in the definitions of the compounds of formula (I) or of any of the subgroups of compounds of formula (I); or in particular R¹⁰ is as defined above; especially R¹⁰ is hydrogen, C₁₋₆alkyl (e.g. methyl, ethyl, isopropyl, tert-butyl), amino, pyrrolidinyl, piperidinyl, piperazinyl, 4-C₁₋₆alkylpiperazinyl (e.g. 4-methylpiperazinyl), morpholinyl, C₁₋₆alkylamino, (C₁₋₆alkyl)₂amino, aminocarbonyl, or mono- or diC₁₋₆alkylaminocarbonyl; and wherein the morpholine and piperidine may optionally substituted with one or two C₁₋₆alkyl radicals.

Also preferably R^{9a} in the isoquinolinyl radical specified under (e-1) or (e-1-a) includes:

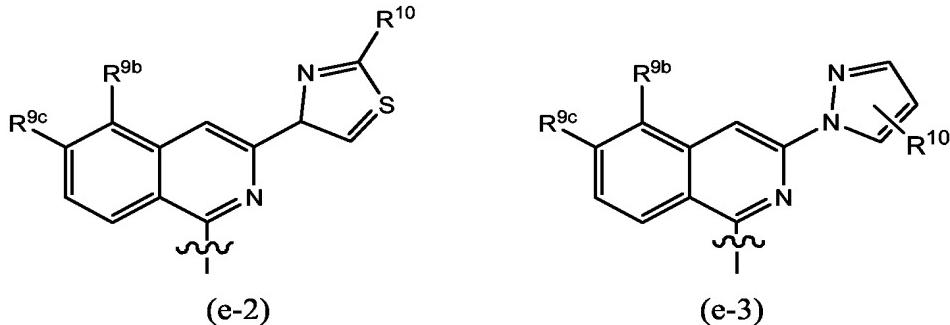


wherein each R¹⁰ is as defined above, and especially is hydrogen, halo, C₁-alkyl (e.g. methyl, ethyl, isopropyl, tert-butyl), amino, pyrrolidinyl, piperidinyl, piperazinyl, 4-C₁-6-alkylpiperazinyl (e.g. 4-methylpiperazinyl), morpholinyl, C₁-6alkylamino, (C₁-6alkyl)₂amino, aminocarbonyl, or mono- or diC₁-6alkylaminocarbonyl; and wherein the morpholinyl, and piperidinyl groups may optionally substituted with one or two C₁-alkyl radicals.

R^{9b} in the isoquinolinyl radical specified under (e-2) may be hydrogen, C₁-alkyl, halo (e.g. bromo, chloro or fluoro), especially hydrogen or bromo.

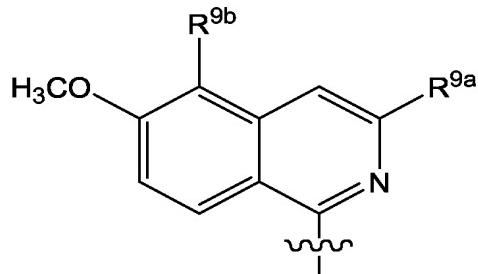
R^{9b} in the isoquinolinyl radical specified under (e-2) may be hydrogen or C₁-alkoxy (e.g. methoxy).

Embodiments of the invention are compounds of formula (I) or any of the subgroups of compounds of formula (I) wherein R¹ is



wherein R^{9b} is hydrogen or halo (e.g. bromo) and R^{9c} is hydrogen or C₁-alkoxy (e.g. methoxy).

Embodiments of the invention are compounds of formula (I) or any of the subgroups of compounds of formula (I) wherein R¹ is

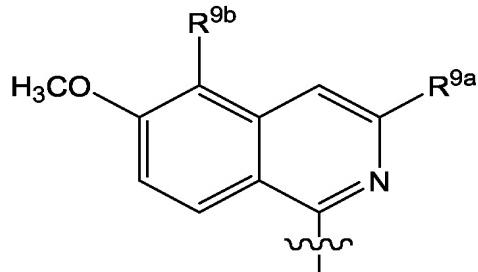


(e-4)

wherein R^{9a} is as defined in any of the groups or subgroups of compounds of formula (I); and

R^{9b} is hydrogen, halo, or trifluoromethyl.

Further preferred embodiments of the invention are compounds of formula (I) or any of the subgroups of compounds of formula (I) wherein R¹ is:

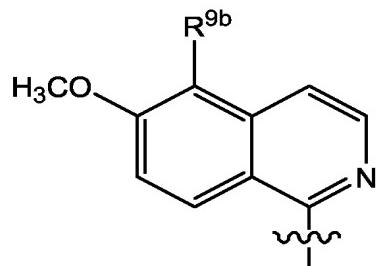


(e-4)

wherein R^{9a} is methoxy, ethoxy or propoxy; and

R^{9b} is hydrogen, fluoro, bromo, chloro, iodo, methyl, ethyl, propyl, or trifluoromethyl.

Further embodiments of the invention are compounds of formula (I) or any of the subgroups of compounds of formula (I) wherein R¹ is:



(e-5)

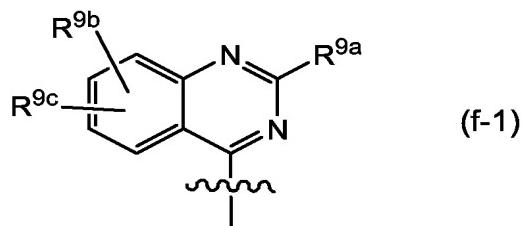
wherein R^{9b} is hydrogen, halo, or trifluoromethyl.

Embodiments of the invention are compounds of formula (I) or any of the subgroups of compounds of formula (I) wherein R¹ is

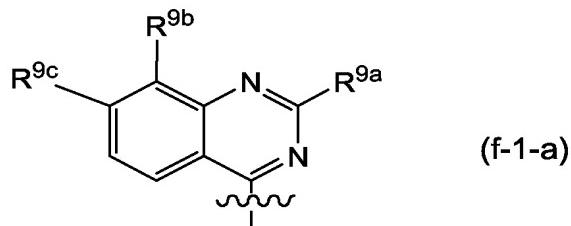
(f) quinazolinyl (in particular quinazolin-4-yl), optionally substituted with 1, 2, 3 or 4 (or with 1, 2 or 3) substituents selected from those mentioned as possible substituents on the monocyclic or bicyclic ring systems of R¹, as specified in the definitions of the compounds of formula (I) or of any of the subgroups of compounds of formula (I).

Quinazoline embodiments of R¹ include

(f-1) a radical :



or in particular (f-1-a) a radical :



wherein R^{9a}, R^{9b} and R^{9c} have the meanings stated above in relation to R¹ being isoquinolinyl (such as in radicals (e-1), (e-1-a), etc).

wherein specifically R^{9a} is C₃₋₇cycloalkyl, aryl or Het, any of which is optionally substituted with one, two or three (in particular with one) R¹⁰; wherein

R¹⁰ is hydrogen, C₁₋₆alkyl, C₃₋₇cycloalkyl, phenyl, pyridyl, thiazolyl, pyrazolyl, pyrrolidinyl, piperidinyl, piperazinyl, 4-methylpiperazinyl, thiomorpholinyl or morpholinyl, aminocarbonyl, mono or di C₁₋₆alkylaminocarbonyl; wherein the piperidinyl, morpholinyl may be optionally substituted with one or two C₁₋₆alkyl radicals; and the phenyl, pyridyl, thiazolyl, pyrazolyl groups may be optionally substituted with 1, 2 or 3 (or with 1 or 2) substituents each independently selected from C₁₋₆alkyl, C₁₋₆alkoxy, halo, amino, mono- or diC₁₋₆alkylamino (in particular selected from C₁₋₆alkyl);

R^{9b} is hydrogen, halogen, C₁₋₆alkyl (preferably methyl), C₃₋₇cycloalkyl, aryl, Het, halo (in particular bromo, chloro or fluoro);

R^{9c} is hydrogen or C₁₋₆alkoxy.

Favoured embodiments of R^{9a} for quinazolines include aryl or Het, especially wherein R^{9a} is phenyl, pyridyl, thiazolyl, oxazolyl or pyrazolyl either of which is optionally substituted with one, two or three (in particular with one) R¹⁰ as defined.

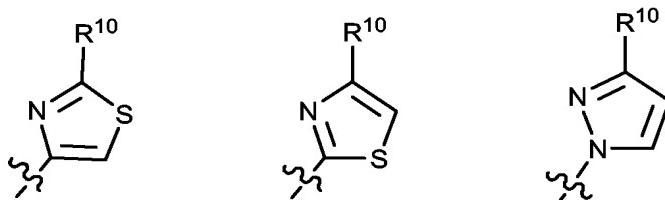
Embodiments of R¹⁰ for quinazoline include is hydrogen, methyl, ethyl, isopropyl, tert-butyl, methoxy, halo (including dihalo, such as difluoro), pyrrolidinyl, piperidinyl, piperazinyl, 4-C₁₋₆alkylpiperazinyl (e.g. 4-methylpiperazinyl) or morpholinyl,

C_{1-6} alkylamino, $(C_{1-6}\text{alkyl})_2\text{amino}$, amino carbonyl, mono or di C_{1-6} alkylamino-carbonyl, or C_{3-7} cycloalkyl (in particular cyclopropyl).

Preferably R^{9a} in the quinazolyl radical specified under (f-1) or (f-1-a) includes any of radicals (q), (q'), (q'-1), (q-1), (q-2), (q-3), (q-4), (q-5), (q-6), (q-7), (q-8) specified above;

wherein R^{10} in these radicals is as defined above or in particular is hydrogen, C_{1-6} alkyl (such as methyl, ethyl, isopropyl, tert-butyl), pyrrolidinyl, piperidinyl, piperazinyl, 4- C_{1-6} alkylpiperazinyl, N-methylpiperazinyl or morpholinyl, C_{1-6} alkylamino, $(C_{1-6}\text{alkyl})_2\text{amino}$ or amino carbonyl, mono or di C_{1-6} alkylaminocarbonyl.

R^{9a} for quinazolines may include



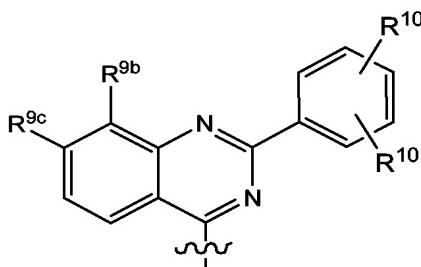
wherein R^{10} is hydrogen, halogen, C_{1-6} alkyl (such as methyl, ethyl, isopropyl, tert-butyl, C_{1-6} alkylamino, $(C_{1-6}\text{alkyl})_2\text{amino}$, C_{1-6} alkylamido, morpholinyl or piperidin-1-yl, the morpholinyl and piperidinyl being optionally substituted with one or two C_{1-6} alkyl groups.

Additional R^{9a} embodiments for quinazolines include phenyl substited with one or two R^{10} groups such as is hydrogen, methyl, ethyl, isopropyl, tert-butyl, methoxy, saturated monocyclic amino, C_{1-6} alkylamino, $(C_{1-6}\text{alkyl})_2\text{amino}$ or aminocarbonyl, mono- and di C_{1-6} alkylaminocarbonyl or halo (in particular fluoro).

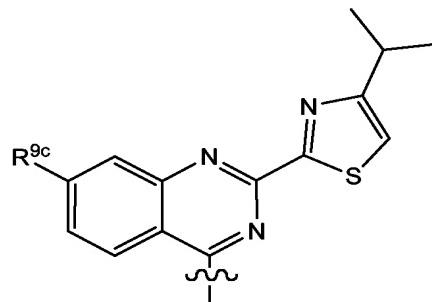
Embodiments of R^{9b} for quinazolines include hydrogen, C_{1-6} alkyl (in particular methyl), halo (e.g. bromo, chloro or fluoro) especially wherein R^{9b} is hydrogen or bromo.

Embodiments of R^{9c} for quinazolines include hydrogen or C_{1-6} alkoxy (in particular methoxy).

Specific embodiments of the compounds of formula (I) or any of the subgroups of compounds of formula (I) are those wherein R^1 is :



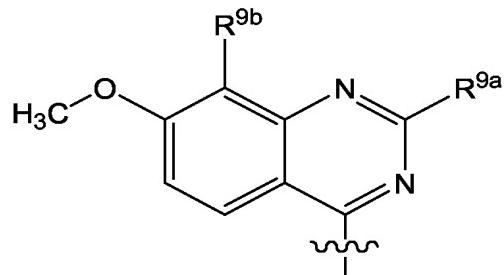
(f-2)



(f-3)

wherein R¹⁰ and R^{9c} are as specified above and in particular and R^{9c} is hydrogen or C₁-alkoxy (e.g. methoxy).

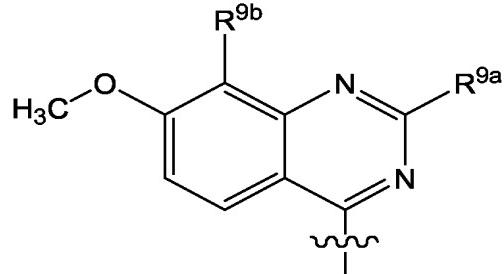
Embodiments of the invention are compounds of formula (I) or any of the subgroups of compounds of formula (I) wherein R¹ is



(g-1)

wherein R^{9a} is as defined in any of the groups or subgroups of compounds of formula (I), preferably R^{9a} is p-methoxyphenyl or p-fluoromethyl; and R^{9b} is hydrogen, methyl, halo, or trifluoromethyl.

Further preferred embodiments of the invention are compounds of formula (I) or any of the subgroups of compounds of formula (I) wherein R¹ is:

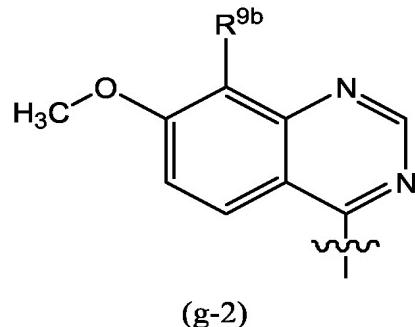


(g-1)

wherein R^{9a} is methoxy, ethoxy or propoxy; and

R^{9b} is hydrogen, fluoro, bromo, chloro, iodo, methyl, ethyl, propyl, or trifluoromethyl.

Further embodiments of the invention are compounds of formula (I) or any of the subgroups of compounds of formula (I) wherein R^1 is:



(g-2)

wherein R^{9b} is hydrogen, halo, or trifluoromethyl.

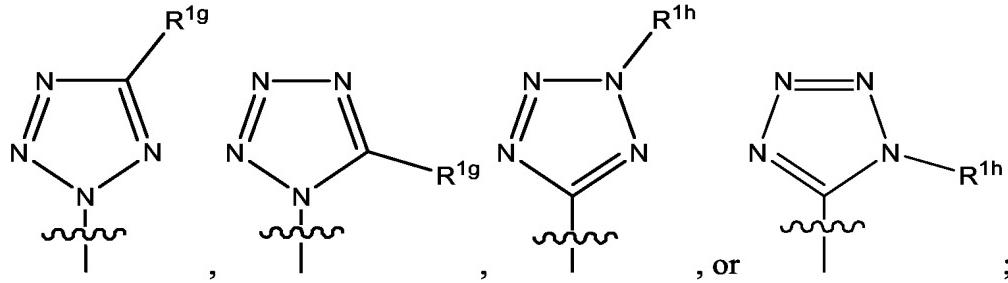
Preferred amongst the subgroups of compounds of the embodiments wherein R^1 is a radical (d-1) – (d-5), (e-1) – (e-3), (f-1) – (f-3), (g-1) – (g-2) as specified above, are those compounds whithin these subgroups wherein is L is –O–.

Embodiments of the invention are compounds of formula (I) or any of the subgroups of compounds of formula (I) wherein L is a direct bond and R^1 is selected from the group consisting of 1*H*-pyrrole, 1*H*-imidazole, 1*H*-pyrazole, furan, thiophene, oxazole, thiazole, isoxazole, isothiazole, pyridine, pyridazine, pyrimidine, pyrazine, phthalazine, quinoxaline, quinazoline, quinoline, cinnoline, 1*H*-pyrrolo[2,3-*b*]pyridine, 1*H*-indole, 1*H*-benzimidazole, 1*H*-indazole, 7*H*-purine, benzothiazole, benzoxazole, 1*H*-imidazo[4, 5-*c*]pyridine, 1*H*-imidazo[4,5-*b*]pyridine, 1, 3-dihydro-benzimidazol-2-one, 1,3-dihydrobenzimidazol-2-thione, 2, 3-dihydro-1*H*-indole, 1,3-dihydro-indol-2-one, 1*H*-indole-2,3-dione, 1*H*-pyrrolo[2, 3-*c*]pyridine, benzofuran, benzo[*b*]thiophene, benzo[*d*]isoxazole, benzo[*d*]isothiazole, 1*H*-quinolin-2-one, 1*H*-quinolin-4-one, 1*H*-quinazolin-4-one, 9*H*-carbazole, and 1*H*-quinazolin-2-one, each optionally substituted with the R^1 substituents specified in the definitions of the compounds of formula (I) or any of the subgroups of compounds of formula (I).

Further embodiments of the invention are compounds of formula (I) or any of the subgroups of compounds of formula (I) wherein L is a direct bond and R^1 is selected from the group consisting of pyrrolidine, 4,5-dihydro-1*H*-pyrazole, pyrazolidine, imidazolidin-2-one, pyrrolidin-2-one, pyrrolidine-2,5-dione, piperidine-2,6-dione, piperidin-2-one, piperazine-2,6-dione, piperazin-2-one, piperazine, morpholine, pyrazolidin-3-one, imidazolidine-2,4-dione, piperidine, tetrahydrofuran,

tetrahydropyran, 1,4-dioxane, and 1,2,3,6-tetrahydropyridine, each optionally substituted with the R¹ substituents specified in the definitions of the compounds of formula (I) or any of the subgroups of compounds of formula (I).

Embodiments of the invention are compounds of formula (I) or any of the subgroups of compounds of formula (I) wherein L is a direct bond and R¹ is optionally substituted tetrazolyl as depicted below:

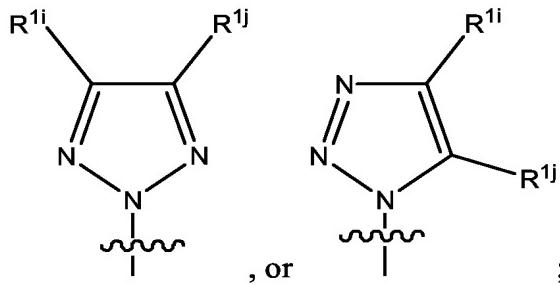


wherein R^{1g} is hydrogen, C₁₋₆alkoxy, hydroxy, -NR^{4a}R^{4b}, -C(=O)R⁶, -SO_pR⁷, C₃₋₇cycloalkyl, aryl, Het, or C₁₋₆alkyl optionally substituted with C₃₋₇cycloalkyl, aryl, or Het;

R^{1h} is hydrogen, -NR^{4a}R^{4b}, C₃₋₇cycloalkyl, aryl, Het, or C₁₋₆alkyl optionally substituted with C₃₋₇cycloalkyl, aryl, or Het; and

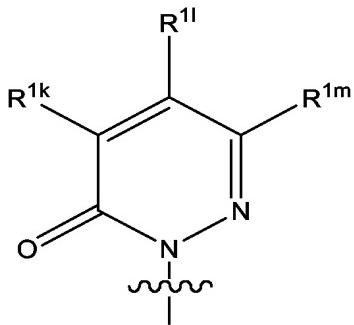
R^{4a}, R^{4b}, R⁶, and R⁷ are as defined above.

Embodiments of the invention are compounds of formula (I) or any of the subgroups of compounds of formula (I) wherein L is a direct bond and R¹ is optionally substituted triazolyl as depicted below:



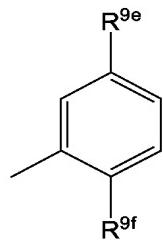
wherein R¹ⁱ and R^{1j} are each, independently, selected from the group consisting of hydrogen, halo, -C(=O)NR^{4a}R^{4b}, -C(=O)R⁶, C₃₋₇cycloalkyl, aryl, Het, and C₁₋₆alkyl optionally substituted with -NR^{4a}R^{4b}, or aryl; or alternatively, R¹ⁱ and R^{1j} taken together with the carbon atoms to which they are attached, may form a cyclic moiety selected from the group consisting of aryl and Het.

Further preferred substituents for R¹ when L is a direct bond, include pyridazinone and derivatives thereof as shown below:



wherein R^{1k}, R¹¹ and R^{1m} are independently selected from the group consisting of hydrogen, azido, halo, C₁-C₆alkyl, -NR^{4a}R^{4b}, C₃₋₇cycloalkyl, aryl, and Het; or alternatively, R^{1k} and R¹¹ or R¹¹ and R^{1m} taken together with the carbon atoms to which they are attached, form a phenyl moiety, which in turn may be optionally substituted with azido, halo, C₁-C₆alkyl, -NR^{4a}R^{4b}, C₃₋₇cycloalkyl, aryl or Het.

Embodiments of the invention are compounds of formula (I) or any of the subgroups of compounds of formula (I) wherein L is -O-(C=O)-NR^{5a}- or in particular wherein L is -O-(C=O)-NH- and R¹ is aryl as defined above; or R¹ is phenyl optionally substituted with 1, 2 or three substituents selected from those mentioned as possible substituents of the radical aryl as in the definitions of the compounds of formula (I) or of any of the subgroups of compounds of formula (I); specifically R¹ is a radical of formula:



wherein

R^{9e} is hydrogen, C₁₋₆alkyl, polyhaloC₁₋₆alkyl or halo;

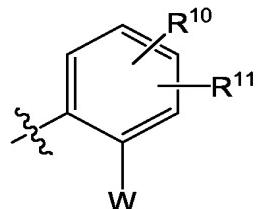
R^{9f} is -COOH, -C(=O)OR^{6a}, halo, Het or aryl; wherein Het and aryl are as defined herein and

R^{6a} is H or C₁₋₆alkyl, preferably R^{6a} is methyl or ethyl;

In particular, R^{9e} may be hydrogen, fluoro or trifluoromethyl.

In particular, R^{9f} may be -COOC₁₋₆alkyl (e.g. -C(=O)OEt), phenyl, thiazolyl, 1-piperidinyl or 1-pyrazolyl, the phenyl, piperidinyl and pyrazolyl groups being optionally substituted with C₁₋₆alkyl, in particular with methyl.

Other embodiments of the invention are compounds of formula (I) or any of the subgroups of compounds of formula (I) wherein L is $-\text{O}(\text{C}=\text{O})\text{-NR}^{5a}\text{-}$ or, in particular, wherein L is $-\text{O}(\text{C}=\text{O})\text{-NH-}$ and R^1 is a radical of formula:



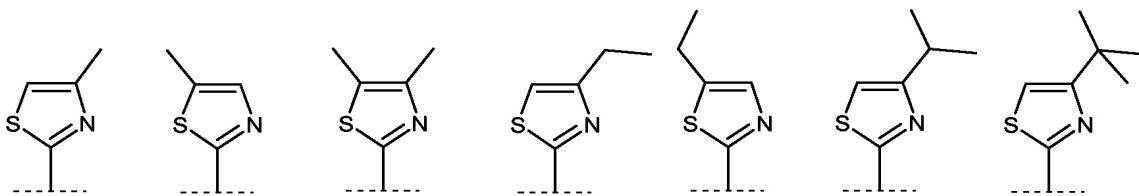
wherein R^{10} and R^{11} independently from one another are hydrogen, halo, hydroxy, nitro, cyano, carboxyl, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkoxy C_{1-6} alkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkoxy-carbonyl, amino, azido, mercapto, C_{1-6} alkylthio, polyhalo C_{1-6} alkyl, aryl or Het; especially R^{10} and R^{11} independently from one another are hydrogen, halo, nitro, carboxyl, methyl, ethyl, isopropyl, t-butyl, methoxy, ethoxy, isopropoxy, t-butoxy, methylcarbonyl, ethylcarbonyl, isopropylcarbonyl, t-butyl-carbonyl, methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, t-butoxycarbonyl, methylthio, ethylthio, isopropylthio, t-butylthio, trifluoromethyl, or cyano;
 W is aryl or Het, or W is $-\text{COOH}$ or $-\text{COOR}^{6a}$, wherein R^{6a} is C_{1-6} alkyl, preferably methyl or ethyl.

Other subgroups of the compounds of formula (I) are those compounds of formula (I), or any subgroup of compounds of formula (I) specified herein, wherein W is phenyl, naphthyl (in particular naphth-1-yl, or naphth-2-yl), pyrrolyl (in particular pyrrol-1-yl), pyridyl (in particular 3-pyridyl), pyrimidinyl (in particular pyrimidin-4-yl), pyridazinyl (in particular pyridazin-3-yl and pyridazin-2-yl), 6-oxo-pyridazin-1-yl, triazolyl (in particular 1,2,3-triazolyl, 1,2,4-triazolyl, more in particular 1,2,3-triazol-2-yl, 1,2,4-triazol-3-yl), tetrazolyl (in particular tetrazol-1-yl, tetrazol-2-yl), pyrazolyl (in particular pyrazol-1-yl, pyrazol-3-yl), imidazolyl (in particular imidazol-1-yl, imidazol-2-yl), thiazolyl (in particular thiazol-2-yl), pyrrolidinyl (in particular pyrrolidin-1-yl), piperidinyl (in particular piperidin-1-yl), piperazinyl (in particular 1-piperazinyl), 4- C_{1-6} alkylpiperazinyl (in particular 4- C_{1-6} alkylpiperazin-1-yl, more in particular 4-methyl-piperazin-1-yl), furanyl (in particular furan-2-yl), thienyl (in particular thien-3-yl), morpholinyl (in particular morpholin-4-yl); all optionally substituted with one or two substituents selected from C_{1-6} alkyl, polyhalo C_{1-6} alkyl, or C_{1-6} alkoxycarbonyl.

In particular W may be phenyl, naphth-1-yl, naphth-2-yl, pyrrol-1-yl, 3-pyridyl, pyrimidin-4-yl, pyridazin-3-yl, pyridazin-2-yl, 6-oxo-pyridazin-1-yl, 1,2,3-triazol-2-yl, 1,2,4-triazol-3-yl, tetrazol-1-yl, tetrazol-2-yl, pyrazol-1-yl, pyrazol-3-yl, imidazol-1-yl,

imidazol-2-yl, thiazol-2-yl, pyrrolidin-1-yl, piperidin-1-yl, furan-2-yl, thien-3-yl, morpholin-4-yl; all optionally substituted with one or two substituents selected from C₁₋₆alkyl, polyhaloC₁₋₆alkyl (such as trifluoromethyl) and C₁₋₆alkoxycarbonyl.

Further subgroups of the compounds of formula (I) are those compounds of formula (I), or any subgroup of compounds of formula (I) specified herein, wherein W is thiazol-2-yl substituted with one or two C₁₋₆alkyl, such as methyl, ethyl, isopropyl or *tert*-butyl. Preferred subgroups of the compounds of formula (I) are those compounds of formula (I), or any subgroup of compounds of formula (I) specified herein, wherein W is selected from the following structures:



Embodiments of the invention are compounds of formula (I) or any of the subgroups of compounds of formula (I) wherein R¹⁰ and R¹¹ independently from one another are hydrogen, halo, nitro, carboxyl, C₁₋₆alkyl, C₁₋₆alkoxy, C₁₋₆alkylcarbonyl, C₁₋₆alkoxy-carbonyl, C₁₋₆alkylthio, polyhaloC₁₋₆alkyl, cyano, aryl or Het.

Embodiments of the invention are compounds of formula (I) or any of the subgroups of compounds of formula (I) wherein R¹⁰ and R¹¹ independently from one another are hydrogen, halo, nitro, carboxyl, methyl, ethyl, isopropyl, *tert*-butyl, methoxy, ethoxy, isopropoxy, *tert*-butoxy, methylcarbonyl, ethylcarbonyl, isopropylcarbonyl, *tert*-butylcarbonyl, methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, *tert*-butoxycarbonyl, methylthio, ethylthio, isopropylthio, *tert*-butylthio, trifluoromethyl, or cyano.

Preferred embodiments of the invention are compounds of formula (I) or any of the subgroups of compounds of formula (I) wherein one of R¹⁰ and R¹¹ is hydrogen.

Preferred embodiments of the invention are compounds of formula (I) or any of the subgroups of compounds of formula (I) wherein one of R¹⁰ and R¹¹ is halo (in particular fluoro), trifluoromethyl or C₁₋₆alkyl (in particular methyl). Other preferred embodiments are those wherein one of R¹⁰ and R¹¹ is halo (in particular fluoro), trifluoromethyl or methyl, and the other of R¹⁰ and R¹¹ is hydrogen.

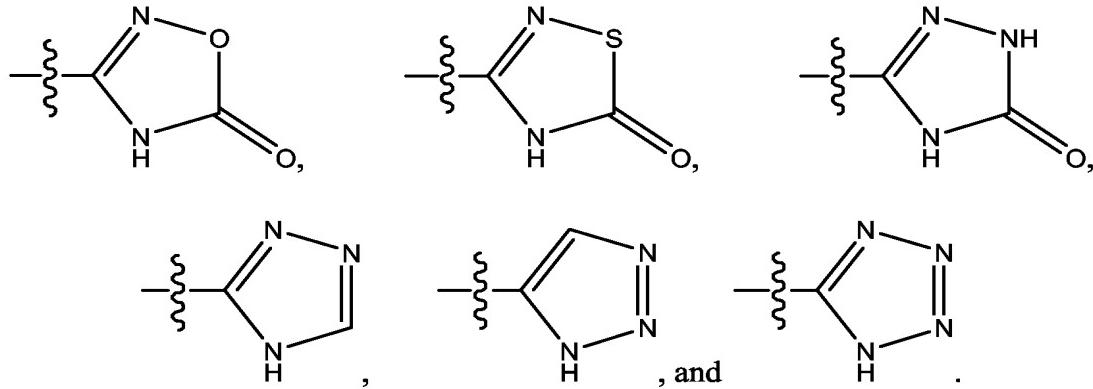
Preferred embodiments of the invention are compounds of formula (I) or any of the subgroups of compounds of formula (I) wherein one of R¹⁰ and R¹¹ is in para position

in respect of the W group. Further preferred embodiments are compounds of formula (I) or any of the subgroups of compounds of formula (I) wherein one of R¹⁰ and R¹¹ is halo (in particular fluoro), trifluoromethyl or methyl, and is in para position in respect of the W group; the other of R¹⁰ and R¹¹ may be as defined above or may be hydrogen.

Embodiments of the invention are compounds of formula (I) or any of the subgroups of compounds of formula (I) wherein

- (a) R² is -NHR^{4c}, in particular wherein R^{4c} is C₁₋₆alkyl, aryl, Het, C₁₋₆alkoxy, -O-aryl, or -O-Het;
- (b) R² is -OR⁵, in particular wherein R⁵ is C₁₋₆alkyl, such as methyl, ethyl, or *tert*-butyl and preferably wherein R⁵ is hydrogen;
- (c) R² is -NHS(=O)₂R⁷, in particular wherein R⁷ is C₁₋₆alkyl, C₃₋₇cycloalkyl optionally substituted with C₁₋₆alkyl, or aryl, e.g. wherein R⁷ is methyl, cyclopropyl, methylcyclopropyl, or phenyl;
- (d) R² is -C(=O)OR⁵, -C(=O)R⁶, -C(=O)NR^{4a}R^{4b}, or -C(=O)NHR^{4c}, wherein R^{4a}, R^{4b}, R^{4c}, R⁵, or R⁶ are as defined above, and R² preferably is -C(=O)NHR^{4c} wherein R^{4c} is cyclopropyl;
- (e) R² is -NHS(=O)₂NR^{4a}R^{4b} in particular wherein R^{4a} and R^{4b} are, each independently, hydrogen, C₃₋₇cycloalkyl or C₁₋₆alkyl, e.g. NHS(=O)₂N(C₁₋₃alkyl)₂.

Further embodiments of the invention are compounds of formula (I) or any of the subgroups of compounds of formula (I) wherein R² is -NHR^{4c}, and R^{4c} is a Het group selected from



Further embodiments of the invention are compounds of formula (I) or any of the subgroups of compounds of formula (I) wherein R² is -NHR^{4c}, and R^{4c} is a C₁₋₆alkyl substituted with -C(=O)OR⁵.

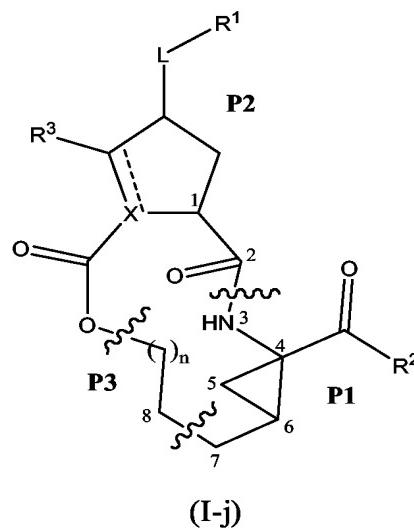
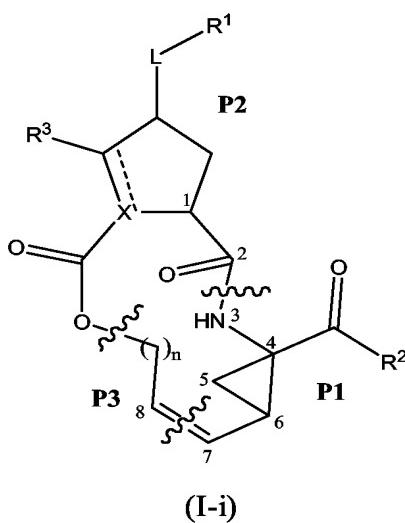
Further embodiments of the invention are compounds of formula (I) or any of the subgroups of compounds of formula (I) wherein

- (a) R³ is hydrogen;
 - (b) R³ is C₁₋₆alkyl, preferably methyl.

Embodiments of the invention are compounds of formula (I) or any of the subgroups of compounds of formula (I) wherein

- (a) X is N, C (X being linked via a double bond) or CH (X being linked via a single bond) and R³ is hydrogen;
 - (b) X is C (X being linked via a double bond) and R³ is C₁₋₆alkyl, preferably methyl.

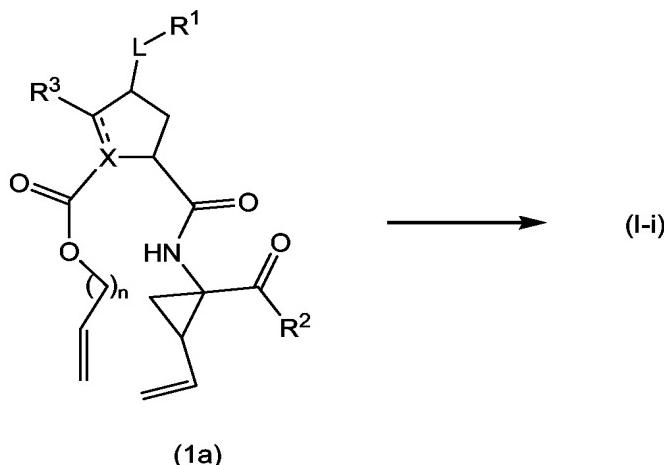
The compounds of formula (I) consist of three building blocks P1, P2, P3, which are each delimited by a curved line. The building block P1 further contains a P1' tail. The linking of building blocks P1 with P2, and optionally P1 with P1', involves forming an amide bond. The linking of building blocks P3 with P2 involves an acylation when P2 is a pyrrolidine ring. The linking of blocks P1 and P3 involves double bond formation. The linking of building blocks P1, P1', P2 and P3 to prepare compounds of formula (I) can be done in any given sequence. One of the steps involves a cyclization whereby the macrocycle is formed. Compounds of formula (I-j) can be prepared from compound of formula (I-i) by a reduction of the double bond, e.g. with hydrogen in the presence of a noble metal catalyst such as Rh, Pd or Pt.



The synthesis procedures described hereinafter are meant to be applicable for as well the racemates, stereochemically pure intermediates or end products, or any stereoisomeric mixtures. The racemates or stereochemical mixtures may be separated into stereoisomeric forms at any stage of the synthesis procedures. In one embodiment, the intermediates and end products have the stereochemistry specified above in the compounds of formula (I-b).

In one embodiment, compounds (I-i) are prepared by first forming the amide bond between P2 and P1, coupling the P3 moiety to P2, and subsequent forming the double bond linkage between P3 and P1 with concomitant cyclization to the macrocycle.

In a preferred embodiment, compounds (I) wherein the bond between C₇ and C₈ is a double bond, which are compounds of formula (I-i), as defined above, may be prepared as outlined in the following reaction scheme:



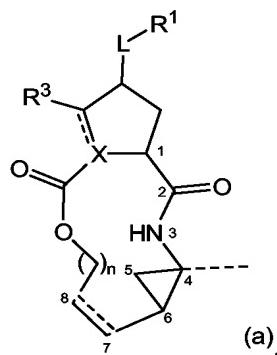
Formation of the macrocycle can be carried out via an olefin metathesis reaction in the presence of a suitable metal catalyst such as e.g. the Ru-based catalyst reported by Miller, S.J., Blackwell, H.E., Grubbs, R.H. J. Am. Chem. Soc. 118, (1996), 9606-9614; Kingsbury, J. S., Harrity, J. P. A., Bonitatebus, P. J., Hoveyda, A. H., J. Am. Chem. Soc. 121, (1999), 791-799; and Huang et al., J. Am. Chem. Soc. 121, (1999), 2674-2678; for example a Hoveyda-Grubbs catalyst.

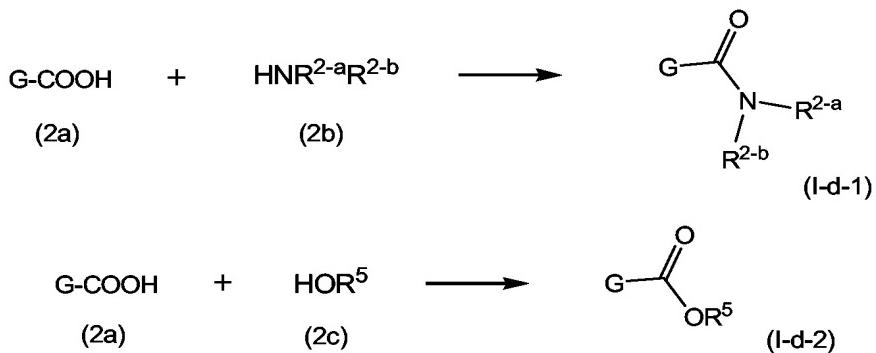
Air-stable ruthenium catalysts such as bis(tricyclohexylphosphine)-3-phenyl-1H-inden-1-ylidene ruthenium chloride (Neolyt M1®) or bis(tricyclohexylphosphine)-[(phenylthio)methylene]ruthenium (IV) dichloride can be used. Other catalysts that can be used are Grubbs first and second generation catalysts, i.e. Benzylidene-bis(tricyclohexylphosphine)dichlororuthenium and (1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(phenylmethylene)-(tricyclohexylphosphine)ruthenium, respectively. Of particular interest are the Hoveyda-Grubbs first and second generation catalysts, which are dichloro(*o*-isopropoxyphenylmethylene)(tricyclohexylphosphine)ruthenium(II) and 1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(*o*-isopropoxyphenylmethylene)ruthenium respectively. Also other catalysts containing other transition metals such as Mo can be used for this reaction.

The metathesis reactions may be conducted in a suitable solvent such as for example ethers, e.g. THF, dioxane; halogenated hydrocarbons, e.g. dichloromethane, CHCl₃, 1,2-dichloroethane and the like, hydrocarbons, e.g. toluene. In a preferred embodiment, the metathesis reaction is conducted in toluene. These reactions are conducted at increased temperatures under nitrogen atmosphere.

Compounds of formula (I) wherein the link between C7 and C8 in the macrocycle is a single bond, i.e. compounds of formula (I-j), can be prepared from the compounds of formula (I-i) by a reduction of the C7-C8 double bond in the compounds of formula (I-i). This reduction may be conducted by catalytic hydrogenation with hydrogen in the presence of a noble metal catalyst such as, for example, Pt, Pd, Rh, Ru or Raney nickel. Of interest is Rh on alumina. The hydrogenation reaction preferably is conducted in a solvent such as, e.g. an alcohol such as methanol, ethanol, or an ether such as THF, or mixtures thereof. Water can also be added to these solvents or solvent mixtures.

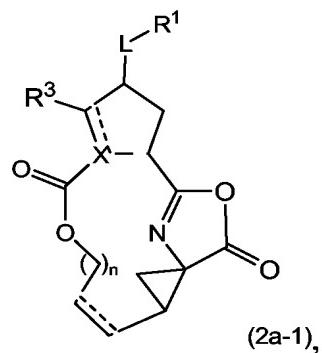
The R² group can be connected to the P1 building block at any stage of the synthesis, i.e. before or after the cyclization, or before or after the cyclization and reduction as described herein above. The compounds of formula (I) wherein R² represents -NR^{4a}R^{4b}, -NHR^{4c}, -NHSO_pNR^{4a}R^{4b}, -NR^{5a}SO_pR⁷, these groups being collectively represented by -NR^{2-a}R^{2-b}, said compounds being represented by formula (I-d-1), can be prepared by linking the R² group to P1 by forming an amide bond between both moieties. Similarly, the compounds of formula (I) wherein R² represents -OR⁵, i.e. compounds (I-d-2), can be prepared by linking the R² group to P1 by forming an ester bond. In one embodiment, the -NR^{2-a}R^{2-b} or -OR⁵ groups are introduced in the last step of the synthesis of the compounds (I) as outlined in the following reaction schemes wherein G represents a group:





Intermediate (2a) can be coupled with the amine (2b) by an amide forming reaction such as any of the procedures for the formation of an amide bond described hereinafter. In particular, (2a) may be treated with a coupling agent, for example *N,N'*-carbonyldiimidazole (CDI), EEDQ, IIDQ, EDCI, or benzotriazol-1-yl-oxy-tris-pyrrolidinophosphonium hexafluorophosphate (commercially available as PyBOP®), in a solvent such as an ether, e.g. THF, or a halogenated hydrocarbon, e.g. dichloromethane, chlorophorm, dichloroethane, followed by reaction with the desired amine (2b), preferably after reacting (2a) with the coupling agent. The reactions of (2a) with (2b) preferably are conducted in the presence of a base, for example a trialkylamine such as triethylamine or diisopropylethylamine, or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Intermediate (2a) can also be converted into an activated form, e.g. an activated form of general formula G-CO-Z, wherein Z represents halo, or the rest of an active ester, e.g. Z is an aryloxy group such as phenoxy, p.nitrophenoxy, pentafluorophenoxy, trichlorophenoxy, pentachlorophenoxy and the like; or Z can be the rest of a mixed anhydride. In one embodiment, G-CO-Z is an acid chloride (G-CO-Cl) or a mixed acid anhydride (G-CO-O-CO-R or G-CO-O-CO-OR, R in the latter being e.g. C₁₋₄alkyl, such as methyl, ethyl, propyl, i.propyl, butyl, t.butyl, i.butyl, or benzyl). The activated form G-CO-Z is reacted with the desired (2b).

The activation of the carboxylic acid in (2a) as described in the above reactions may lead to an internal cyclization reaction to an azalactone intermediate of formula

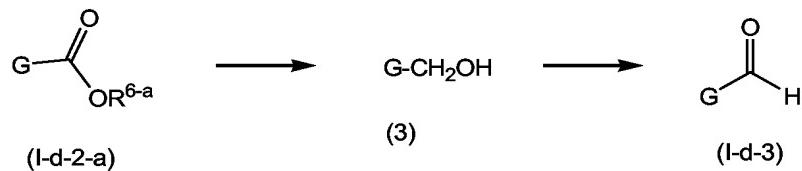


wherein L, R¹, R³, n are as specified above and wherein the stereogenic centers may have the stereochemical configuration as specified above, for example as in (I-a) or (I-b). The intermediates (2a-1) can be isolated from the reaction mixture, using conventional methodology, and the isolated intermediate (2a-1) is then reacted with (2b), or the reaction mixture containing (2a-1) can be reacted further with (2b) without isolation of (2a-1). In one embodiment, where the reaction with the coupling agent is conducted in a water-immiscible solvent, the reaction mixture containing (2a-1) may be washed with water or with slightly basic water in order to remove all water-soluble side products. The thus obtained washed solution may then be reacted with (2b) without additional purification steps. The isolation of intermediates (2a-1) on the other hand may provide certain advantages in that the isolated product, after optional further purification, may be reacted with (2b), giving rise to less side products and an easier work-up of the reaction.

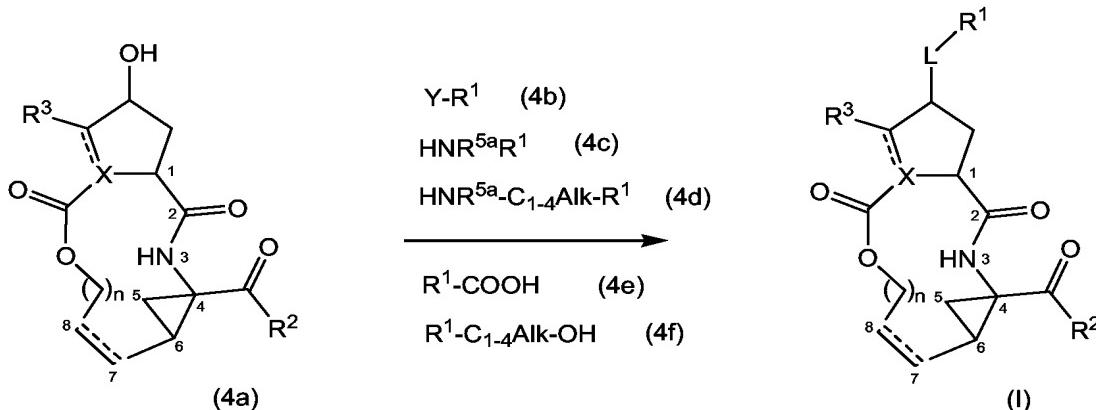
Intermediate (2a) can be coupled with the alcohol (2c) by an ester forming reaction. For example, (2a) and (2c) are reacted together with removal of water either physically, e.g. by azeotropical water removal, or chemically by using a dehydrating agent.

Intermediate (2a) can also be converted into an activated form G-CO-Z, such as the activated forms mentioned above, and subsequently reacted with the alcohol (2c). The ester forming reactions preferably are conducted in the presence of a base such as an alkali metal carbonate or hydrogen carbonate, e.g. sodium or potassium hydrogen carbonate, or a tertiary amine such as the amines mentioned herein in relation to the amide forming reactions, in particular a trialkylamine, e.g. triethylamine. Solvents that can be used in the ester forming reactions comprise ethers such as THF; halogenated hydrocarbons such as dichloromethane, CHCl₃; hydrocarbons such as toluene; polar aprotic solvents such as DMF, DMSO, DMA; and the like solvents.

The compounds of formula (I) wherein R² represents hydrogen, i.e. compounds (I-d-3), can be prepared as follows. First, the esters (I-d-2-a), which are intermediates of formula (I-d-2) wherein R⁶ is C₁₋₄alkyl, are reduced to the corresponding alcohols (3), e.g. with a complex metal hydride such as LiAlH₄ or NaBH₄, followed by an oxidation reaction with a mild oxidant, e.g. with MnO₂, thus obtaining intermediates (I-d-3).



The compounds of formula (I) can also be prepared by reacting an intermediate (4a) with intermediates (4b) – (4f) as outlined in the following reaction scheme wherein the various radicals have the meanings specified above and C₁₋₄Alk represents C₁₋₄alkanediyl:



Y in (4b) represents hydroxy or a leaving group such as a halide, e.g. bromide or chloride, or an arylsulfonyl group, e.g. mesylate, triflate or tosylate and the like.

In one embodiment, the reaction of (4a) with (4b) is an O-arylation reaction and Y represents a leaving group. This reaction can be conducted following the procedures described by E. M. Smith et al. (J. Med. Chem. (1988), 31, 875-885). In particular, this reaction is conducted in the presence of a base, preferably a strong base, in a reaction-inert solvent, e.g. one of the solvents mentioned for the formation of an amide bond.

In a particular embodiment, starting material (4a) is reacted with (4b) in the presence of a base which is strong enough to detract a hydrogen from the hydroxyl group, for example an alkali or alkaline metal hydride such as LiH or sodium hydride, or alkali metal alkoxide such as sodium or potassium methoxide or ethoxide, potassium *tert*-butoxide, in a reaction inert solvent like a dipolar aprotic solvent, e.g. DMA, DMF and the like. The resulting alcoholate is reacted with the arylating agent (4b), wherein Y is a suitable leaving group as mentioned above. The conversion of (4a) to (I) using this type of O-arylation reaction does not change the stereochemical configuration at the carbon bearing the hydroxyl or -L-R¹ group.

Alternatively, the reaction of (4a) with (4b) can also be conducted via a Mitsunobu reaction (Mitsunobu, 1981, Synthesis, January, 1-28; Rano et al., Tetrahedron Lett., 1995, 36, 22, 3779-3792; Krchnak et al., Tetrahedron Lett., 1995, 36, 5, 6193-6196; Richter et al., Tetrahedron Lett., 1994, 35, 27, 4705-4706). This reaction comprises treatment of intermediate (4a) with (4b) wherein Y is hydroxyl, in the presence of triphenylphosphine and an activating agent such as a dialkyl azocarboxylate, e.g.

diethyl azodicarboxylate (DEAD), diisopropyl azodicarboxylate (DIAD) or the like. The Mitsunobu reaction changes the stereochemical configuration at the carbon bearing the hydroxy or -L-R¹ group.

Compounds of formula (I) wherein L is a urethane group (L is -O-C(=O)-NR^{5a}-) can be prepared by reacting (4a) with (4c) or (4d) in the presence of a carbonyl introducing agent. The latter comprise reagents such as phosgene or phosgene derivatives such as carbonyl diimidazole (CDI). In one embodiment, (4a) is reacted with phosgene thus providing the corresponding chloroformate which upon reaction with an amine, R¹-NH₂, or H-NR¹R^{5a}, provides carbamates i.e. L is -OC(=O)NH- or -OC(=O)NR^{5a}- . The reactions of the chloroformate with the amine preferably are conducted using the same solvents and bases as those mentioned for an amide bond formation, mentioned hereinafter, in particular those mentioned in relation to the reaction of (2a) with (2b). Particular bases are alkali metal carbonates or hydrogen carbonates, e.g. sodium or potassium hydrogen carbonate, or tertiary amines, such as a trialkylamine, e.g. triethylamine.

The reaction of alcohol (4a) with an acid (4e) yields ester derivatives of formula (4a), i.e. L is -O-C(=O)-. Standard procedures for ester formation can be used, in particular those described above in relation to the reaction of (2a) with (2c). These e.g. may involve converting the acid (4e) into an active form such as an acid anhydride or acid halide, for instance an acid chloride (R¹-C(=O)Cl), and reacting the active form with the alcohol (4a).

Compounds of formula (I) wherein L is -O-C₁₋₄alkanediyl-, can be prepared by an ether forming reaction with (4f). Ether formation can be by azeotropical water removal, or chemically, e.g. by a Williamson reaction.

Alternatively, in order to prepare the compounds of formula (I), first an amide bond between building blocks P2 and P1 is formed, followed by coupling of the P3 building block to the P1 moiety in P1-P2, and a subsequent carbamate or ester bond formation between P3 and the P2 moiety in P2-P1-P3 with concomitant ring closure.

Yet another alternative synthetic methodology is the formation of an amide bond between building blocks P2 and P3, followed by the coupling of building block P1 to the P3 moiety in P3-P2, and a last amide bond formation between P1 and P2 in P1-P3-P2 with concomitant ring closure.

Building blocks P1 and P3 can be linked and the thus formed P1-P3 block can be coupled to building block P2 and the thus forming sequence P1-P2-P3 subsequently cyclized, by forming carbamate or ester amide bonds.

Building blocks P1 and P3 in any of the previous approaches can be linked via double bond formation, e.g. by the olefin metathesis reaction described hereinafter, or a Wittig type reaction. If desired, the thus formed double bond can be reduced, similarly as describe above for the conversion of (I-i) to (I-j). The double bond can also be reduced at a later stage, i.e. after addition of a third building block, or after formation of the macrocycle. Building blocks P2 and P1 are linked by amide bond formation and P3 and P2 are linked by carbamate or ester formation.

The tail P1' can be bonded to the P1 building block at any stage of the synthesis of the compounds of formula (I), for example before or after coupling the building blocks P2 and P1; before or after coupling the P3 building block to P1; or before or after ring closure.

The individual building blocks can first be prepared and subsequently coupled together or alternatively, precursors of the building blocks can be coupled together and modified at a later stage to the desired molecular composition.

The functionalities in each of the building blocks may be protected to avoid side reactions.

The formation of amide bonds can be carried out using standard procedures such as those used for coupling amino acids in peptide synthesis. The latter involves the dehydrative coupling of a carboxyl group of one reactant with an amino group of the other reactant to form a linking amide bond. The amide bond formation may be performed by reacting the starting materials in the presence of a coupling agent or by converting the carboxyl functionality into an active form such as an active ester, mixed anhydride or a carboxyl acid chloride or bromide. General descriptions of such coupling reactions and the reagents used therein can be found in general textbooks on peptide chemistry, for example, M. Bodanszky, "Peptide Chemistry", 2nd rev. ed., Springer-Verlag, Berlin, Germany, (1993).

Examples of coupling reactions with amide bond formation include the azide method, mixed carbonic-carboxylic acid anhydride (isobutyl chloroformate) method, the carbodiimide (dicyclohexylcarbodiimide, diisopropylcarbodiimide, or water-soluble carbodiimide such as *N*-ethyl-*N'*-[(3-dimethylamino)propyl]carbodiimide) method, the

active ester method (e.g. *p*-nitrophenyl, *p*-chlorophenyl, trichlorophenyl, pentachlorophenyl, pentafluorophenyl, *N*-hydroxysuccinic imido and the like esters), the Woodward reagent K-method, the 1,1-carbonyldiimidazole (CDI or N,N'-carbonyl-diimidazole) method, the phosphorus reagents or oxidation-reduction methods. Some of these methods can be enhanced by adding suitable catalysts, e.g. in the carbodiimide method by adding 1-hydroxybenzotriazole, DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), or 4-DMAP. Further coupling agents are (benzotriazol-1-yloxy)tris-(dimethylamino) phosphonium hexafluorophosphate, either by itself or in the presence of 1-hydroxybenzotriazole or 4-DMAP; or 2-(1*H*-benzotriazol-1-yl)-*N,N,N',N'*-tetra-methyluronium tetrafluoroborate, or O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate. These coupling reactions can be performed in either solution (liquid phase) or solid phase.

A preferred amide bond formation is performed employing N-ethyloxycarbonyl-2-ethyloxy-1,2-dihydroquinoline (EEDQ) or N-isobutyloxy-carbonyl-2-isobutyloxy-1,2-dihydroquinoline (IIDQ). Unlike the classical anhydride procedure, EEDQ and IIDQ do not require base nor low reaction temperatures. Typically, the procedure involves reacting equimolar amounts of the carboxyl and amine components in an organic solvent (a wide variety of solvents can be used). Then EEDQ or IIDQ is added in excess and the mixture is allowed to stir at room temperature.

The coupling reactions preferably are conducted in an inert solvent, such as halogenated hydrocarbons, e.g. dichloromethane, chloroform, dipolar aprotic solvents such as acetonitrile, dimethylformamide, dimethylacetamide, DMSO, HMPT, ethers such as tetrahydrofuran (THF).

In many instances the coupling reactions are done in the presence of a suitable base such as a tertiary amine, e.g. triethylamine, diisopropylethylamine (DIPEA), *N*-methylmorpholine, *N*-methylpyrrolidine, 4-DMAP or 1,8-diazabicycle[5.4.0]undec-7-ene (DBU). The reaction temperature may range between 0 °C and 50 °C and the reaction time may range between 15 min and 24 h.

The functional groups in the building blocks that are linked together may be protected to avoid formation of undesired bonds. Appropriate protecting groups that can be used are listed for example in Greene, "Protective Groups in Organic Chemistry", John Wiley & Sons, New York (1999) and "The Peptides: Analysis, Synthesis, Biology", Vol. 3, Academic Press, New York (1987).

Carboxyl groups can be protected as an ester that can be cleaved off to give the carboxylic acid. Protecting groups that can be used include 1) alkyl esters such as methyl, trimethylsilyl and *tert*-butyl; 2) arylalkyl esters such as benzyl and substituted benzyl; or 3) esters that can be cleaved by a mild base or mild reductive means such as trichloroethyl and phenacyl esters.

Amino groups can be protected by a variety of N-protecting groups, such as:

- 1) acyl groups such as formyl, trifluoroacetyl, phthalyl, and *p*-toluenesulfonyl;
- 2) aromatic carbamate groups such as benzyloxycarbonyl (Cbz or Z) and substituted benzyloxycarbonyls, and 9-fluorenylmethyloxycarbonyl (Fmoc);
- 3) aliphatic carbamate groups such as *tert*-butyloxycarbonyl (Boc), ethoxycarbonyl, diisopropylmethoxy-carbonyl, and allyloxycarbonyl;
- 4) cyclic alkyl carbamate groups such as cyclopentyloxycarbonyl and adamantlyloxycarbonyl;
- 5) alkyl groups such as triphenylmethyl, benzyl or substituted benzyl such as 4-methoxybenzyl;
- 6) trialkylsilyl such as trimethylsilyl or t.Bu dimethylsilyl; and
- 7) thiol containing groups such as phenylthiocarbonyl and dithiasuccinoyl.

Interesting amino protecting groups are Boc and Fmoc.

Preferably the amino protecting group is cleaved off prior to the next coupling step. Removal of N-protecting groups can be done following art-known procedures. When the Boc group is used, the methods of choice are trifluoroacetic acid, neat or in dichloromethane, or HCl in dioxane or in ethyl acetate. The resulting ammonium salt is then neutralized either prior to the coupling or in situ with basic solutions such as aqueous buffers, or tertiary amines in dichloromethane or acetonitrile or dimethyl-formamide. When the Fmoc group is used, the reagents of choice are piperidine or substituted piperidine in dimethylformamide, but any secondary amine can be used. The deprotection is carried out at a temperature between 0 °C and room temperature, usually around 15-25 °C, or 20-22 °C.

Other functional groups that can interfere in the coupling reactions of the building blocks may also be protected. For example hydroxyl groups may be protected as benzyl or substituted benzyl ethers, e.g. 4-methoxybenzyl ether, benzoyl or substituted benzoyl esters, e.g. 4-nitrobenzoyl ester, or with trialkylsilyl groups (e.g. trimethylsilyl or *tert*-butyldimethylsilyl).

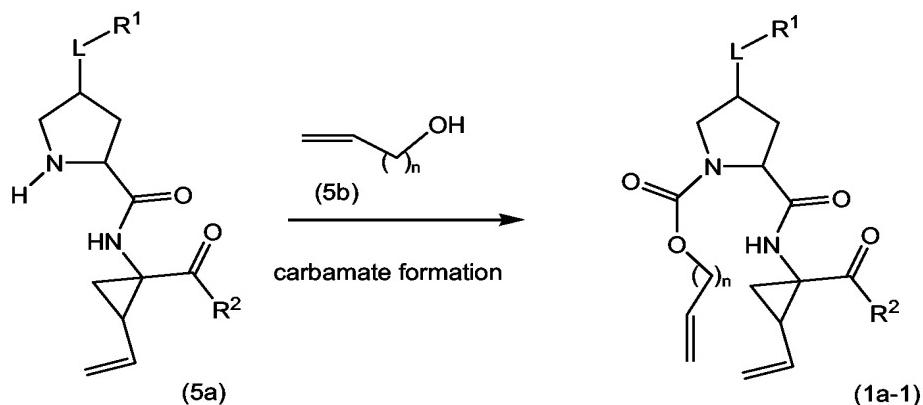
Further amino groups may be protected by protecting groups that can be cleaved off selectively. For example, when Boc is used as the α-amino protecting group, the

following side chain protecting groups are suitable: p-toluenesulfonyl (tosyl) moieties can be used to protect further amino groups; benzyl (Bn) ethers can be used to protect hydroxy groups; and benzyl esters can be used to protect further carboxyl groups. Or when Fmoc is chosen for the α -amino protection, usually *tert*-butyl based protecting groups are acceptable. For instance, Boc can be used for further amino groups; *tert*-butyl ethers for hydroxyl groups; and *tert*-butyl esters for further carboxyl groups.

Any of the protecting groups may be removed at any stage of the synthesis procedure but preferably, the protecting groups of any of the functionalities not involved in the reaction steps are removed after completion of the build-up of the macrocycle.

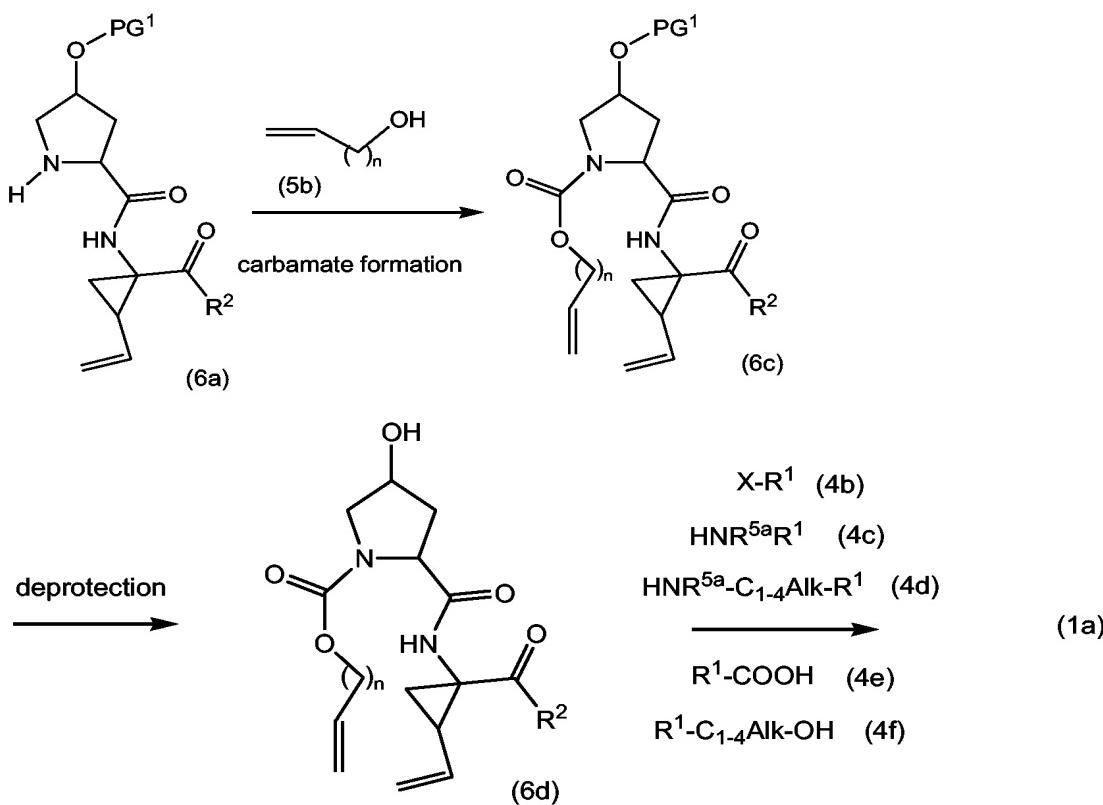
Removal of the protecting groups can be done in whatever manner is dictated by the choice of protecting groups, which manners are well known to those skilled in the art.

The intermediates of formula (1a) wherein X is N, said intermediates being represented by formula (1a-1), may be prepared by a carbamate forming reaction starting from intermediates (5a) which are reacted with a carbamate forming reagent derived from alkenol (5b) as outlined in the following reaction scheme.



Intermediates (5a) are reacted with the said carbamate forming reagent using the same solvents and bases as those used for the amide bond formation as described above.

The intermediates (1a-1) can alternatively be prepared as follows:



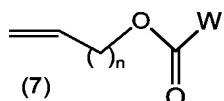
PG¹ is an O-protecting group, which can be any of the groups mentioned herein and in particular is a benzoyl or substituted benzoyl group such as 4-nitrobenzoyl.

Intermediates (6a) are reacted with a carbamate forming reagent derived from alkenyl (5b) and this reaction yields intermediates (6c). These are deprotected, in particular using the reaction conditions mentioned above. For example where PG¹ is benzoyl or substituted benzoyl this group is removed by reaction with a an alkali metal hydroxide (LiOH, NaOH, KOH), in particular where PG¹ is 4-nitrobenzoyl, with LiOH, in an aqueous medium comprising water and a water-soluble organic solvent such as an alkanol (methanol, ethanol) and THF. The resulting alcohol (6d) is reacted with intermediates (4b) – (4f) as described above for the reaction of (4a) with (4b) – (4f) and this reaction results in intermediates (1a).

Carbamate forming reactions may be conducted using a variety of methods, in particular by reaction of amines with alkyl chloroformates; by reaction of alcohols with carbamoyl chlorides or isocyanates; via reactions involving metal complexes or acyl transfer agents. See for example, Greene, T. W. and Wuts, P. G. M., "Protective Groups in Organic Synthesis"; 1999; Wiley and Sons, p. 309-348. Carbon monoxide and certain metal catalysts can be used to synthesize carbamates from several starting compounds, including amines. Metals such as palladium, iridium, uranium, and

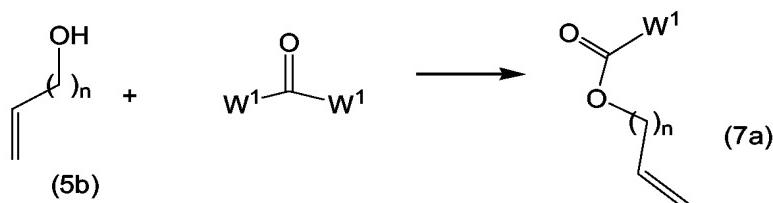
platinum may be used as catalysts. Methods using carbon dioxide for synthesis of carbamates that have been also been reported, can also be used (see for example, Yoshida, Y., et al., *Bull. Chem. Soc. Japan* 1989, 62, 1534; and Aresta, M., et al., *Tetrahedron*, 1991, 47, 9489).

One approach for the preparation of carbamates is by using a reagent

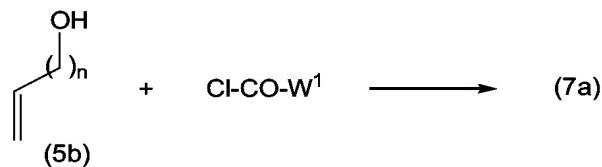


wherein W is leaving group such as halo, in particular chloro and bromo, or a group used in active esters for amide bond formation, such as those mentioned above, for example phenoxy or substituted phenoxy such as p.chloro and p.nitrophenoxy, trichlorophenoxy, pentachlorophenoxy, N-hydroxy-succinimidyl, and the like. Reagent (7) can be formed from alkenol (5b) and phosgene thus forming an alkenyl chloroformate or by transferring the chloro in the latter to reagents (7) wherein W is W¹, the latter being any of the active ester moieties such as those mentioned above, hereafter referred to as reagents (7a). Reagents (7) are reacted with (5a) or (6a), obtaining (1a-1) or (6c).

The reagents (7a) can also be prepared by reacting alkenols (5b) with carbonates W¹-CO-W¹ such as e.g. bisphenol, bis-(substituted phenol) or bis N-hydroxy-succinimidyl carbonates:

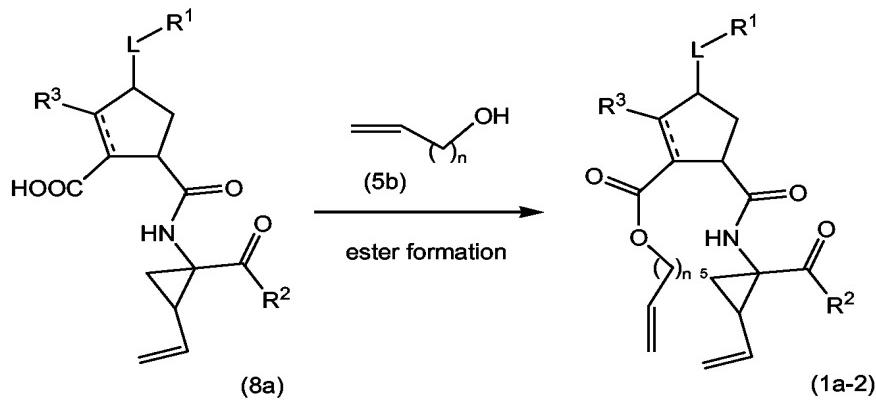


The reagents (7a) may also be prepared from chloroformates Cl-CO-W¹ as follows:

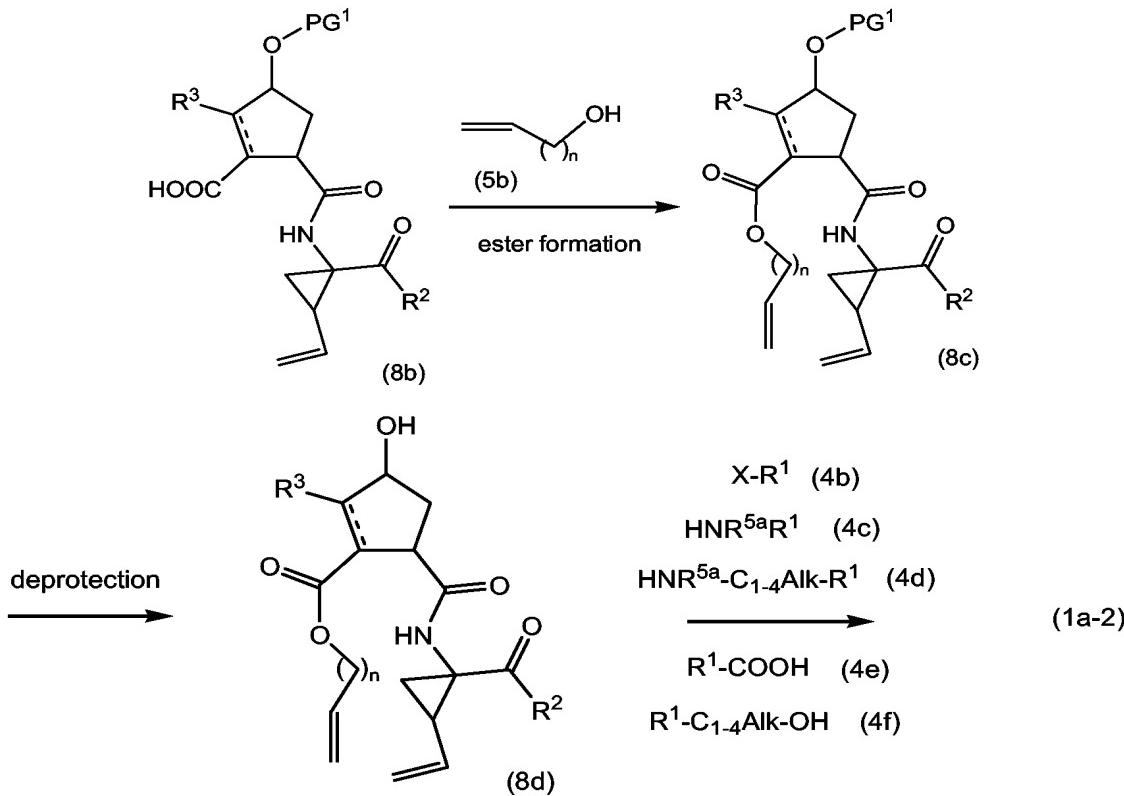


The above reactions to prepare reagents (7a) may be conducted in the presence of a suitable base and in a reaction-inert solvent such as the bases and solvents mentioned above for the synthesis of amide bonds, in particular triethylamine and dichloromethane.

The intermediates of formula (1a) wherein X is C, said intermediates being represented by formula (1a-2), may be prepared by an ester forming reaction starting from an intermediates (8a) which are reacted with an alkenol (5b) as shown in the following reaction scheme, using reaction conditions for preparing esters such as the reaction conditions as those described above for the reaction of (4a) with (4e).



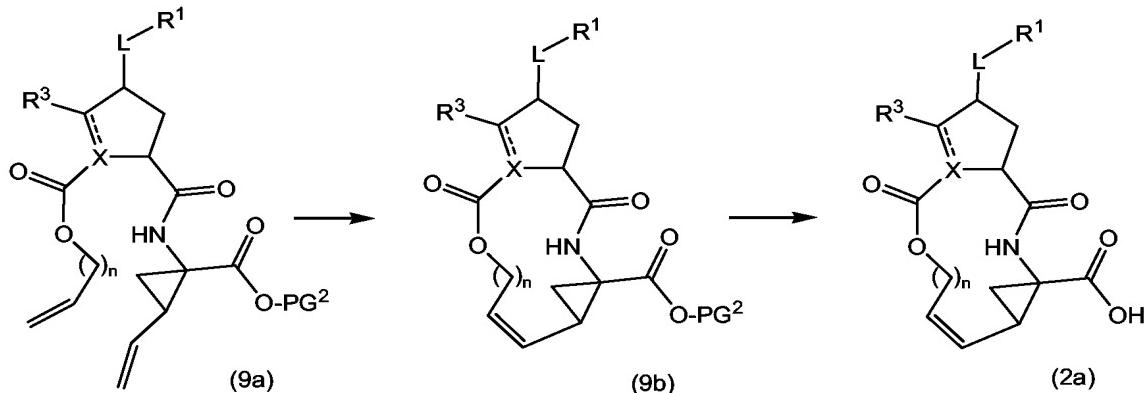
The intermediates (1a-1) can alternatively be prepared as follows:



PG¹ is an O-protecting group as described above. The same reaction conditions as described above may be used: ester formation as for the reaction of (4a) with (4e),

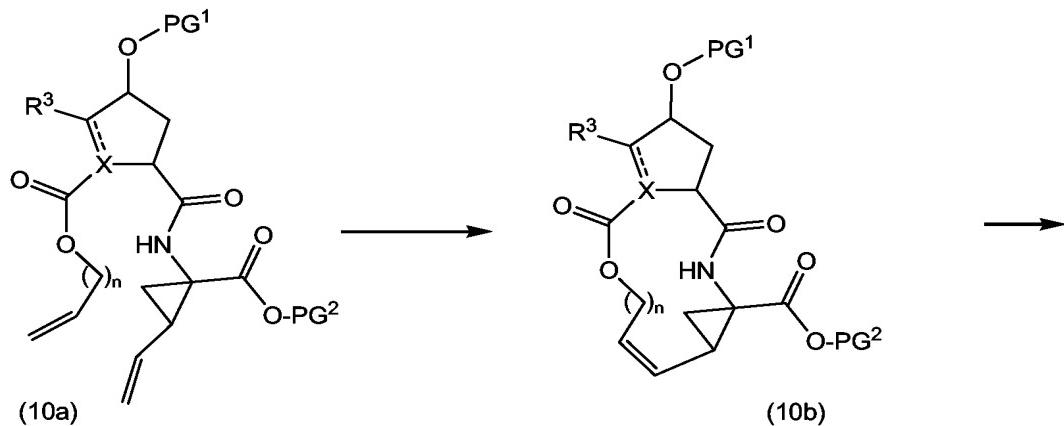
removal of PG¹ as in the description of the protecting groups and introduction of R¹ as in the reactions of (4a) with the reagents (4b) -(4f).

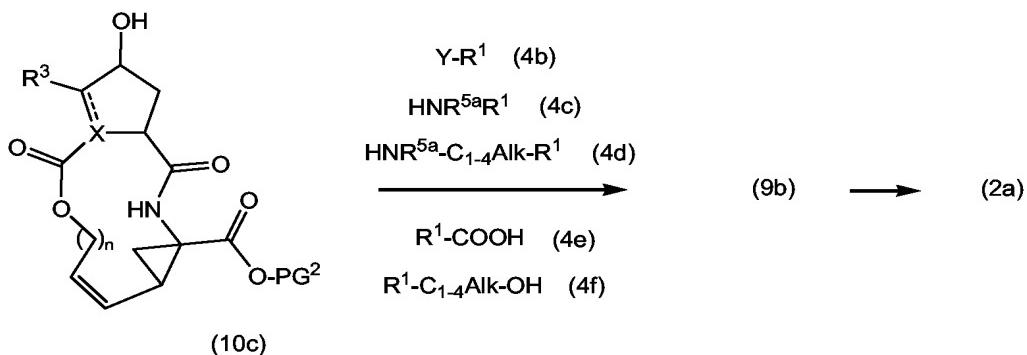
The intermediates of formula (2a) may be prepared by first cyclizing the open ester (9a) to a macrocyclic ester (9b), which in turn is converted to (2a) as follows:



L-R¹ is as specified above and PG² is a carboxyl protecting group, e.g. one of the carboxyl protecting groups mentioned above, in particular a C₁₋₄alkyl or benzyl ester, e.g. a methyl, ethyl or t.butyl ester. The reaction of (9a) to (9b) is a metathesis reaction and is conducted as described above. The group PG² is removed following procedures also described above. Where PG¹ is a C₁₋₄alkyl ester, it is removed by alkaline hydrolysis, e.g. with NaOH or preferably LiOH, in an aqueous solvent, e.g. a C₁₋₄alkanol/water mixture. A benzyl group can be removed by catalytic hydrogenation.

In an alternative synthesis, intermediates (2a) can be prepared as follows:

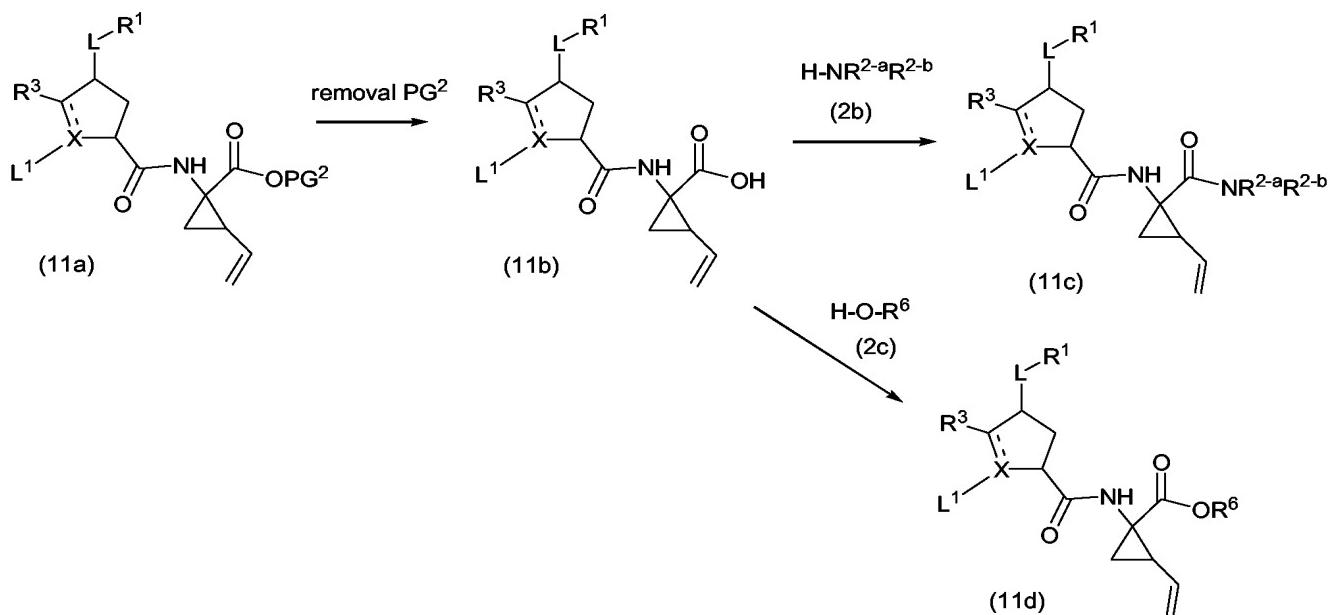




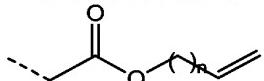
The PG^1 group is selected such that it is selectively cleavable towards PG^2 . PG^2 may be e.g. methyl or ethyl esters, which can be removed by treatment with an alkali metal hydroxide in an aqueous medium, in which case PG^1 e.g. is t.butyl or benzyl. PG^2 may be t.butyl esters removable under weakly acidic conditions or PG^1 may be benzyl esters removable with strong acid or by catalytic hydrogenation, in the latter two cases PG^1 e.g. is a benzoic ester such as a 4-nitrobenzoic ester.

First, intermediates (10a) are cyclized to the macrocyclic esters (10b), the latter are deprotected by removal of the PG^1 group to (10c), which are reacted with intermediates (4b) – (4f) to intermediates (9b), followed by removal of carboxyl protecting group PG^2 , which yields intermediates (2a). The cyclization, deprotection of PG^1 and PG^2 and the coupling with (4b) – (4f) are as described above.

The R^2 groups can be introduced at any stage of the synthesis, either as the last step as described above, or earlier, before the macrocycle formation. In the following scheme the group R^2 being $-\text{NR}^{2-a}\text{R}^{2-b}$ (which is as specified above), or R^2 being $-\text{OR}^6$ are introduced:



In the above scheme, L and PG^2 are as defined above and L^1 is a P3 group

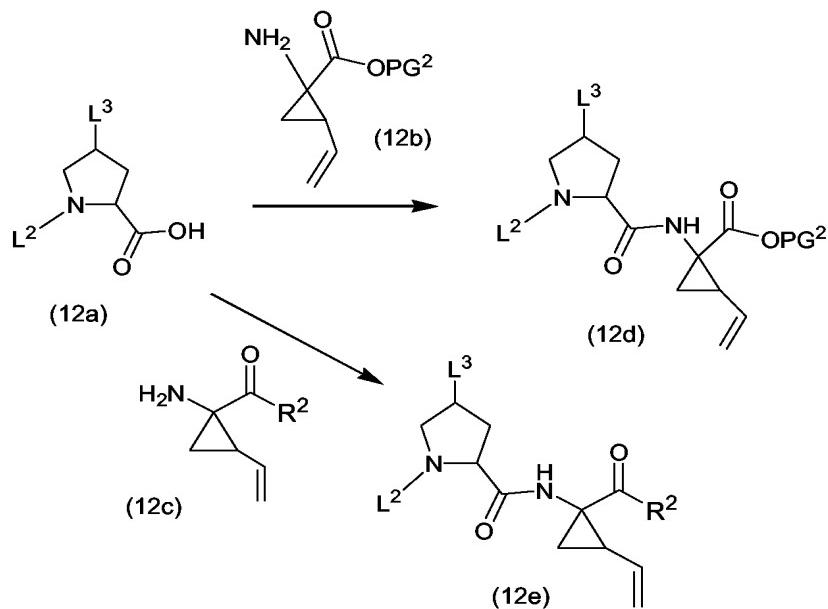


(b), wherein n is as defined above and where X is N, L¹ may also be a nitrogen-protecting group (PG, as defined above) and where X is C, L¹ may also be a group -COOPG^{2a}, wherein the group PG^{2a} is a carboxyl protecting group as PG², but wherein PG^{2a} is selectively cleavable towards PG². In one embodiment PG^{2a} is t.butyl and PG² is methyl or ethyl.

The intermediates (11c) and (11d) wherein L¹ represents a group (b) correspond to the intermediates (1a) and may be processed further as specified above.

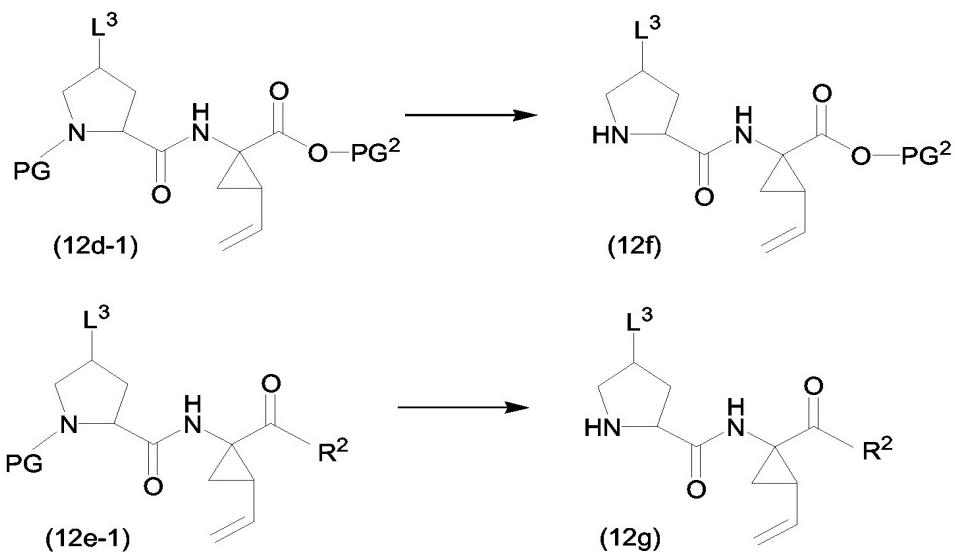
Coupling of P1 and P2 building blocks

The P1 and P2 building blocks are linked using an amide forming reaction following the procedures described above. The P1 building block may have a carboxyl protecting group PG² (as in (12b)) or may already be linked to P1' group (as in (12c)). L² is a N-protecting group (PG), or a group (b), as specified above. L³ is hydroxy, -OPG¹ or a group -L-R¹ as specified above. Where in any of the following reaction schemes L³ is hydroxy, prior to each reaction step, it may be protected as a group -OPG¹ and, if desired, subsequently deprotected back to a free hydroxy function. Similarly as described above, the hydroxy function may be converted to a group -L-R¹.



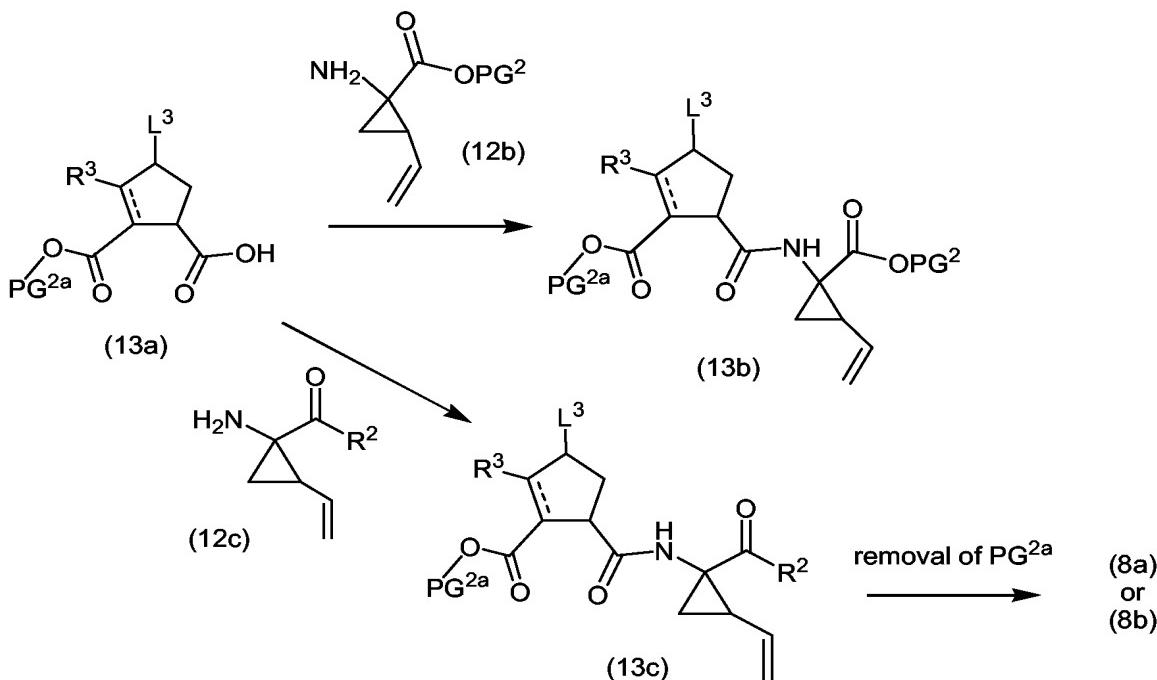
In the procedure of the above scheme, a cyclopropyl amino acid (12b) or (12c) is coupled to the acid function of the P2 building block (12a) with the formation of an amide linkage, following the procedures described above. Intermediates (12d) or (12e) are obtained. Where in the latter L² is a group (b), the resulting products are P3-P2-P1 sequences encompassing some of the intermediates (11c) or (11d) in the previous reaction scheme. Removal of the acid protecting group in (12d), using the appropriate conditions for the protecting group used, followed by coupling with an amine HNR²⁻^aR^{2-b} (2b) or with HOR⁶ (2c) as described above, again yields the intermediates (12e), wherein -COR² are amide or ester groups. Where L² is a N-protecting group, it can be removed yielding intermediates (5a) or (6a). In one embodiment, PG in this reaction is a BOC group and PG² is methyl or ethyl. Where additionally L³ is hydroxy, the starting material (12a) is Boc-L-hydroxyproline. In a particular embodiment, PG is BOC, PG² is methyl or ethyl and L³ is -L-R¹.

In one embodiment, L² is a group (b) and these reactions involve coupling P1 to P2-P3, which results in the intermediates (1a-1) or (1a) mentioned above. In another embodiment, L² is a N-protecting group PG, which is as specified above, and the coupling reaction results in intermediates (12d-1) or (12e-1), from which the group PG can be removed, using reaction conditions mentioned above, obtaining intermediates (12-f) or respectively (12g), which encompass intermediates (5a) and (6a) as specified above:

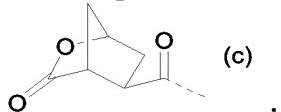


In one embodiment, the group L³ in the above schemes represents a group -O-PG¹ which can be introduced on a starting material (12a) wherein L³ is hydroxy. In this instance PG¹ is chosen such that it is selectively cleavable towards group L² being PG.

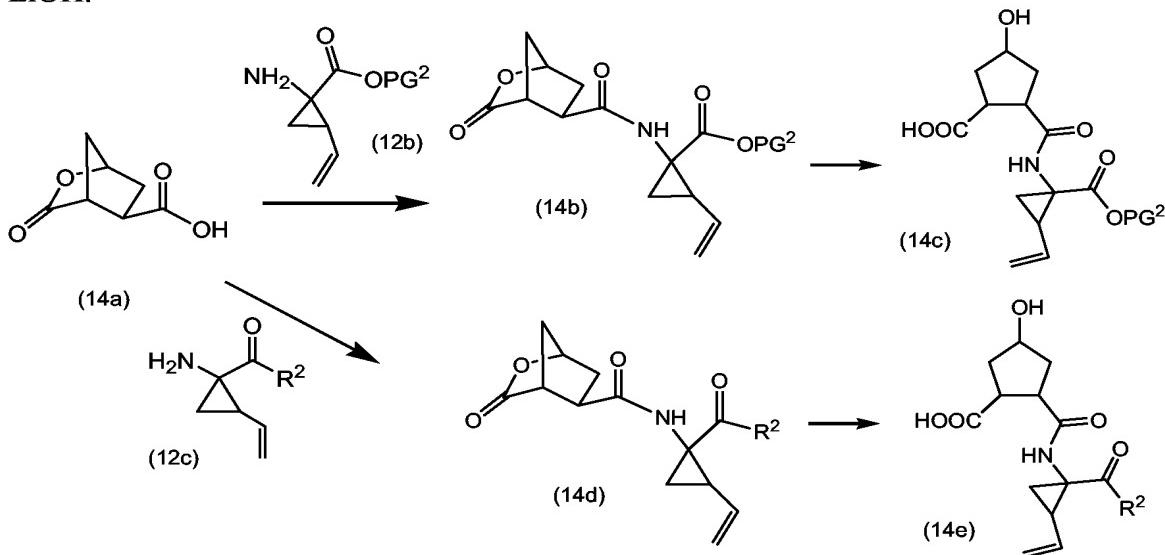
In a similar way, P2 building blocks wherein X is C, which are cyclopentane or cyclopentene derivatives, can be linked to P1 building blocks as outlined in the following scheme wherein R², R³, L³, PG² and PG^{2a} are carboxyl protecting groups. PG^{2a} typically is chosen such that it is selectively cleavable towards group PG². Removal of the PG^{2a} group in (13c) yields intermediates (8a) or (8b), which can be reacted with (5b) as described above.



In one particular embodiment, where X is C, R³ is H, and where X and the carbon bearing R³ are linked by a single bond (P2 being a cyclopentane moiety), PG^{2a} and L³ taken together form a bond and the P2 building block is represented by formula:



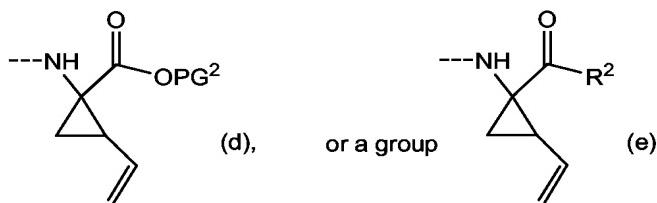
Bicyclic acid (14a) is reacted with (12b) or (12c) similar as described above to (14b) and (14c) respectively, wherein the lactone is opened giving intermediates (14c) and (14e). The lactones can be opened using ester hydrolysis procedures, for example using basic conditions such as an alkali metal hydroxide, e.g. NaOH, KOH, in particular LiOH.

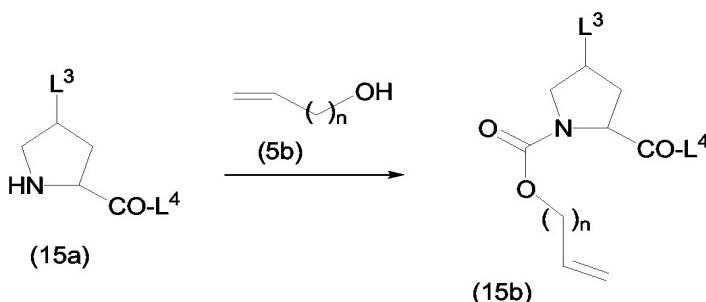


Intermediates (14c) and (14e) can be processed further as described hereinafter.

Coupling of P3 and P2 building blocks

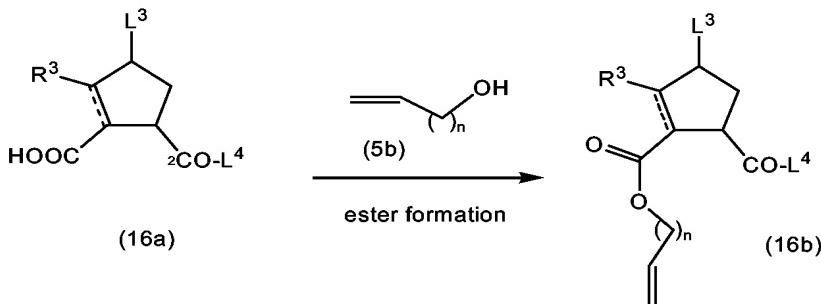
For P2 building blocks that have a pyrrolidine moiety, the P3 and P2 or P3 and P2-P1 building blocks are linked using a carbamate forming reaction following the procedures described above for the coupling of (5a) with (5b). A general procedure for coupling P2 blocks having a pyrrolidine moiety is represented in the following reaction scheme wherein L³ is as specified above and L⁴ is a group -O-PG², a group





In one embodiment L^4 in (15a) is a group $-OPG^2$, the PG^2 group may be removed and the resulting acid coupled with cyclopropyl amino acids (12a) or (12b), yielding intermediates (12d) or (12e) wherein L^2 is a radical (d) or (e).

A general procedure for coupling P3 blocks with a P2 block or a with a P2-P1 block wherein the P2 is a cyclopentane or cyclopentene is shown in the following scheme.



The reactions in the above two schemes are conducted using the same procedures as described above for the reactions of (5a), (8a) or (8b) with (5b) and in particular the above reactions wherein L^4 is a group (d) or (e) correspond to the reactions of (5a), (8a) or (8b) with (5b), described above.

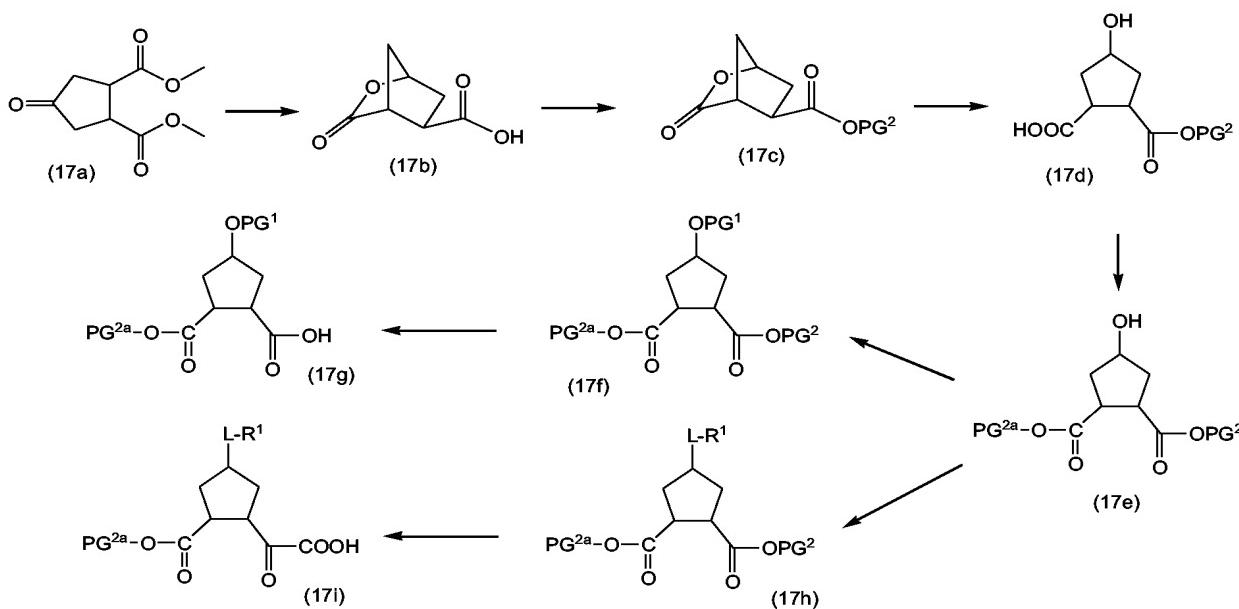
The building blocks P1, P1', P2 and P3 used in the preparation of the compounds of formula (I) can be prepared starting from art-known intermediates. A number of such syntheses are described hereafter in more detail.

Synthesis of P2 building blocks

The P2 building blocks contain either a pyrrolidine, a cyclopentane, or a cyclopentene moiety substituted with a group $-L-R^1$.

P2 building blocks containing a pyrrolidine moiety can be derived from commercially available hydroxy proline.

The preparation of P² building blocks that contain a cyclopentane ring may be performed as shown in the scheme below.

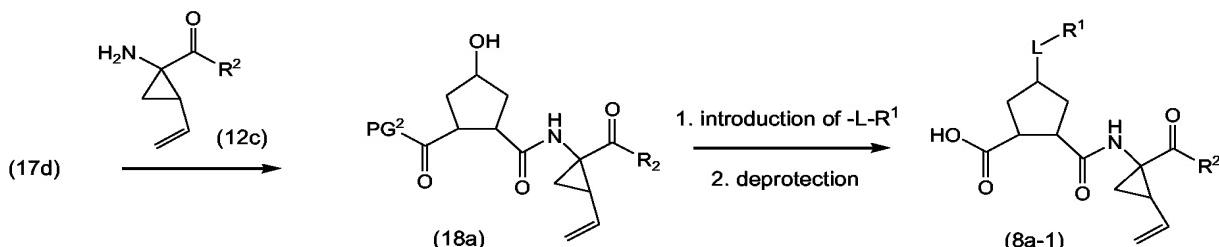


The bicyclic acid (17b) can be prepared, for example, from 3,4-bis(methoxycarbonyl)-cyclopentanone (17a), as described by Rosenquist et al. in Acta Chem. Scand. 46 (1992) 1127-1129. A first step in this procedure involves the reduction of the keto group with a reducing agent like sodium borohydride in a solvent such as methanol, followed by hydrolysis of the esters and finally ring closure to the bicyclic lactone (17b) using lactone forming procedures, in particular by using acetic anhydride in the presence of a weak base such as pyridine. The carboxylic acid functionality in (17b) can then be protected by introducing an appropriate carboxyl protecting group, such as a group PG², which is as specified above, thus providing bicyclic ester (17c). The group PG² in particular is acid-labile such as a t-butyl group and is introduced e.g. by treatment with isobutene in the presence of a Lewis acid or with di-*tert*-butyl dicarbonate in the presence of a base such as a tertiary amine like dimethylamino-pyridine or triethylamine in a solvent like dichloromethane. Lactone opening of (17c) using reaction conditions described above, in particular with lithium hydroxide, yields the acid (17d), which can be used further in coupling reactions with P1 building blocks. The free acid in (17d) may also be protected, preferably with an acid protecting group PG^{2a} that is selectively cleavable towards PG², and the hydroxy function may be converted to a group -OPG¹ or to a group -L-R¹. The products obtained upon removal of the group PG² are intermediates (17g) and (17i) which correspond to intermediates (13a) or (16a) specified above.

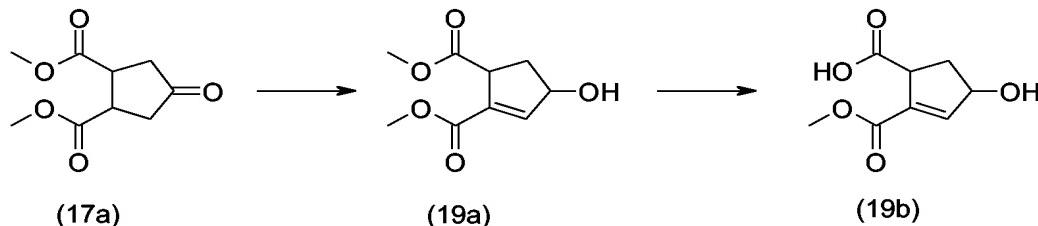
Intermediates with specific stereochemistry may be prepared by resolving the intermediates in the above reaction sequence. For example, (17b) may be resolved following art-known procedures, e.g. by salt form action with an optically active base

or by chiral chromatography, and the resulting stereoisomers may be processed further as described above. The OH and COOH groups in (17d) are in cis position. Trans analogs can be prepared by inverting the stereochemistry at the carbon bearing the OH function by using specific reagents in the reactions introducing OPG¹ or LR¹ that invert the stereochemistry, such as, e.g. by applying a Mitsunobu reaction.

In one embodiment, the intermediates (17d) are coupled to P1 blocks (12b) or (12c), which coupling reactions correspond to the coupling of (13a) or (16a) with the same P1 blocks, using the same conditions. Subsequent introduction of a -L-R¹-substituent as described above followed by removal of the acid protection group PG² yields intermediates (8a-1), which are a subclass of the intermediates (8a), or part of the intermediates (16a). The reaction products of the PG² removal can be further coupled to a P3 building block. In one embodiment PG² in (17d) is t.butyl which can be removed under acidic conditions, e.g. with trifluoroacetic acid.

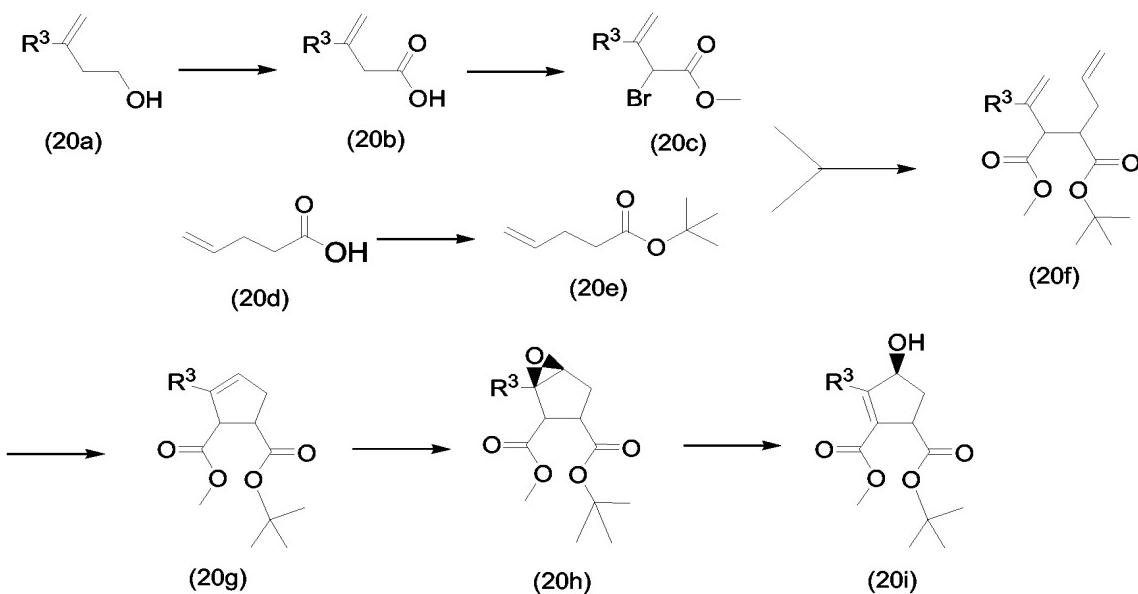


An unsaturated P2 building block, i.e. a cyclopentene ring, may be prepared as illustrated in the scheme below.



A bromination-elimination reaction of 3,4-bis(methoxycarbonyl)cyclopentanone (17a) as described by Dolby et al. in J. Org. Chem. 36 (1971) 1277-1285 followed by reduction of the keto functionality with a reducing agent like sodium borohydride provides the cyclopentenol (19a). Selective ester hydrolysis using for example lithium hydroxide in a solvent like a mixture of dioxane and water, provides the hydroxy substituted monoester cyclopentenol (19b).

An unsaturated P2 building block wherein R³ can also be other than hydrogen, may be prepared as shown in the scheme below.



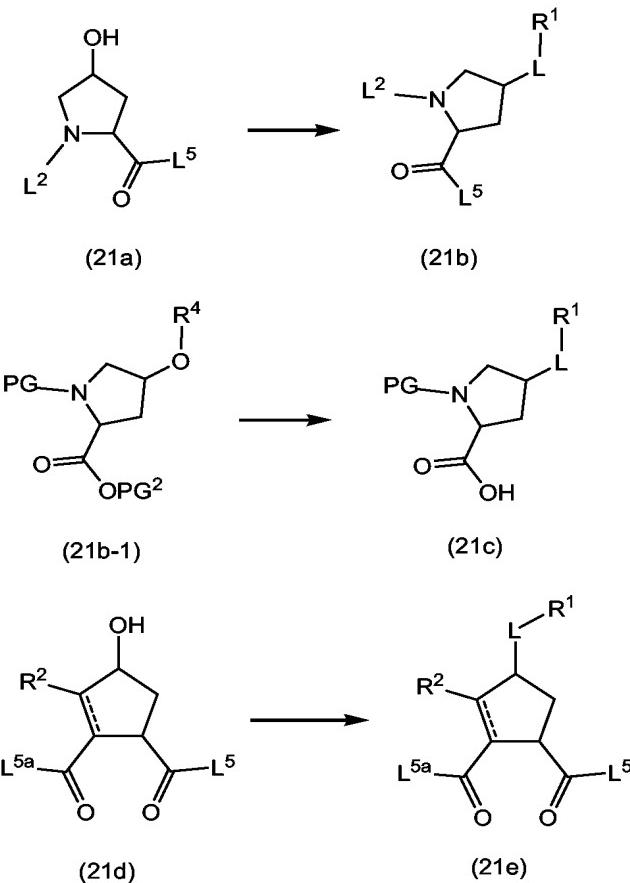
Oxidation of commercially available 3-methyl-3-buten-1-ol (20a), in particular by an oxidizing agent like pyridinium chlorochromate, yields (20b), which is converted to the corresponding methyl ester, e.g. by treatment with acetyl chloride in methanol, followed by a bromination reaction with bromine yielding the α -bromo ester (20c). The latter can then be condensed with the alkenyl ester (20e), obtained from (20d) by an ester forming reaction. The ester in (20e) preferably is a *t*.butyl ester which can be prepared from the corresponding commercially available acid (20d), e.g. by treatment with di-*tert*-butyl dicarbonate in the presence of a base like dimethylaminopyridine. Intermediate (20e) is treated with a base such as lithium diisopropyl amide in a solvent like tetrahydrofuran, and reacted with (20c) to give the alkenyl diester (20f). Cyclisation of (20f) by an olefin metathesis reaction, performed as described above, provides cyclopentene derivative (20g). Stereoselective epoxidation of (20g) can be carried out using the Jacobsen asymmetric epoxidation method to obtain epoxide (20h). Finally, an epoxide opening reaction under basic conditions, e.g. by addition of a base, in particular DBN (1,5-diazabicyclo-[4.3.0]non-5-ene), yields the alcohol (20i). Optionally, the double bond in intermediate (20i) can be reduced, for example by catalytic hydrogenation using a catalyst like palladium on carbon, yielding the corresponding cyclopentane compound. The *t*.butyl ester may be removed to the corresponding acid, which subsequently is coupled to a P1 building block.

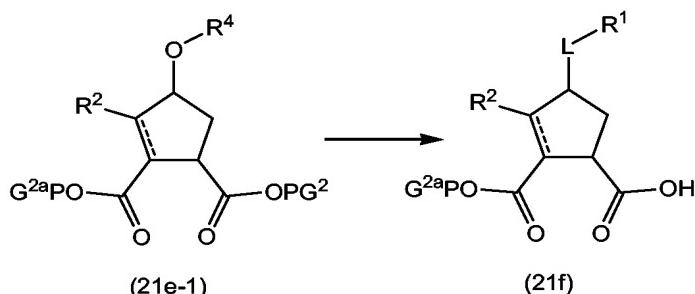
The $-L-R^1$ group can be introduced on the pyrrolidine, cyclopentane or cyclopentene rings at any convenient stage of the synthesis of the compounds according to the present invention. One approach is to first introduce the R^1 group to the said rings and subsequently add the other desired building blocks, i.e. P1 (optionally with the P1' tail) and P3, followed by the macrocycle formation. Another approach is to couple the

building blocks P2, bearing no $-L-R^1$ substituent, with each P1 and P3, and to add the $-L-R^1$ group either before or after the macrocycle formation. In the latter procedure, the P2 moieties have a hydroxy group, which may be protected by a hydroxy protecting group PG¹.

The $-L-R^1$ -groups can be introduced on building blocks P2 by reacting hydroxy substituted intermediates (21a) or (21b) with intermediates (4b) – (4f) as described above for the synthesis of (I) starting from (4a). These reactions are represented in the schemes below, wherein L² is as specified above and L⁵ and L^{5a} independently from one another, represent hydroxy, a carboxyl protecting group -OPG² or -OPG^{2a}, or L⁵ may also represent a P1 group such as a group (d) or (e) as specified above, or L^{5a} may also represent a P3 group such as a group (b) as specified above. The groups PG² and PG^{2a} are as specified above. Where the groups L⁵ and L^{5a} are PG² or PG^{2a}, they are chosen such that each group is selectively cleavable towards the other. For example, one of L⁵ and L^{5a} may be a methyl or ethyl group and the other a benzyl or t.butyl group.

In one embodiment in (21a), L² is PG and L⁵ is -OPG², or in (21d), L^{5a} is -OPG² and L⁵ is -OPG² and the PG² groups are removed as described above.

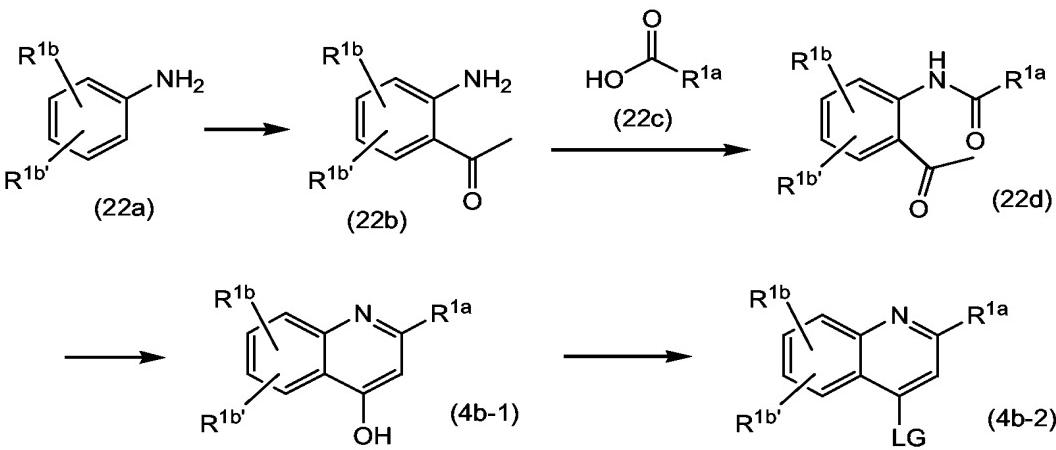




In another embodiment the group L^2 is BOC, L^5 is hydroxy and the starting material (21a) is the commercially available BOC-hydroxyproline, or any other stereoisomeric form thereof, e.g. BOC-L-hydroxyproline, in particular the trans isomer of the latter. Where L^5 in (21b) is a carboxyl-protecting group, it may be removed following procedures described above to (21c). In still another embodiment PG in (21b-1) is Boc and PG² is a lower alkyl ester, in particular a methyl or ethyl ester. Hydrolysis of the latter ester to the acid can be done by standard procedures, e.g. acid hydrolysis with hydrochloric acid in methanol or with an alkali metal hydroxide such as NaOH, in particular with LiOH. In another embodiment, hydroxy substituted cyclopentane or cyclopentene analogs (21d) are converted to (21e), which, where L^5 and L^{5a} are -OPG² or -OPG^{2a}, may be converted to the corresponding acids (21f) by removal of the group PG². Removal of PG^{2a} in (21e-1) leads to similar intermediates.

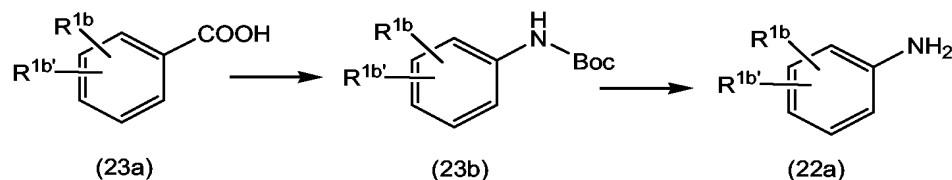
The intermediates (4b), (4c), (4d), (4e) and (4f) are art-known compounds or can be prepared following art-known methods using known starting materials.

Intermediates (4b), which are quinoline derivatives, may be prepared as shown in the scheme below. Such intermediates (4b) for example are those wherein R¹ is a radical (d-1), (d-2), (d-3), (d-4), (d-4-a), (d-5) or (d-5-a) as specified above



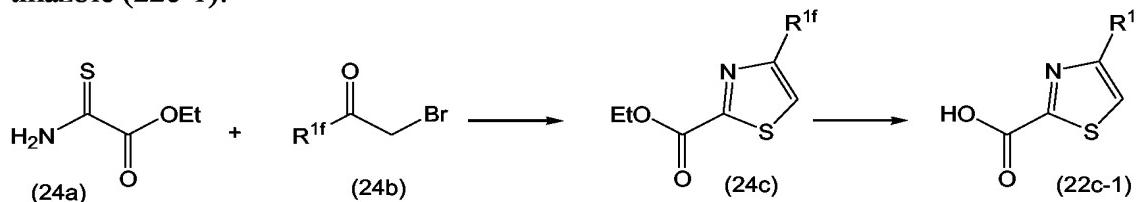
Friedel-Craft acylation of a 3-methoxyaniline (22a), available either commercially or via art-known procedures, using an acylating agent such as acetyl chloride or the like, in the presence of one or more Lewis acids such as boron trichloride or aluminium trichloride, in a solvent like dichloromethane, provides (22b). Coupling of (22b) with 4-isopropyl-thiazole-2-carboxylic acid (22c), preferably under basic conditions, such as in pyridine, in the presence of an activating agent for the carboxylate group, for instance POCl_3 , followed by ring closure and dehydration under basic conditions like potassium *tert*-butoxide in *tert*-butanol yields quinoline derivative (4b-1). The latter can be converted to (4b-2) wherein LG is a leaving group, e.g. by reaction of (4b-1) with a halogenating agent, for example phosphoryl chloride or the like, or by reaction of (4b-1) with an arylsulfonyl chloride, e.g. with tosyl chloride.

Substituted anilines (22a) are available commercially or may be prepared from a suitable substituted benzoic acid (23a), which is reacted with diphenylphosphorylazide at increased temperature and subsequently treated with a C₁₋₄alkanol, in particular t-butanol, affording C₁₋₄alkoxycarbonylamines such as compound (23b). Deprotection of compound (23b) yields substituted anilines (22a).



Alternatively, substituted anilines (22a) may be prepared from the corresponding substituted nitrobenzenes by reducing the latter with elemental zinc, tin or iron in the presence of an acid.

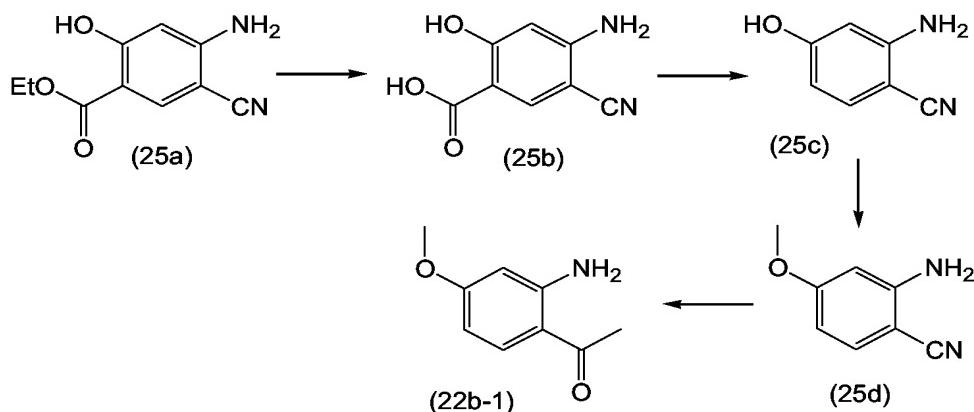
A variety of carboxylic acids with the general structure (22c) can be used in the above synthesis. These acids are available either commercially or can be prepared via art-known procedures. An example of the preparation of 2-(substituted)aminocarboxy-aminothiazole derivatives (22c-1), following the procedure described by Berdikhina et al. in Chem. Heterocycl. Compd. (Engl. Transl.) (1991), 427-433, is shown the following reaction scheme which illustrates the preparation of 2-carboxy-4-isopropyl-thiazole (22c-1):



Ethyl thioxoxamate (24a) is reacted with the β -bromoketone (24b) to form the thiazolyl carboxylic acid ester (24c) which is hydrolyzed to the corresponding acid (22c-1). The ethyl ester in these intermediates may be replaced by other carboxyl protecting groups PG², as defined above. In the above scheme R^{1f} is as defined above and in particular is C₁₋₄alkyl, more in particular i.propyl.

The bromoketone (24b) may be prepared from 3-methyl-butan-2-one (MIK) with a sililating agent (such as TMSCl) in the presence of a suitable base (in particular LiHMDS) and bromine.

Intermediates (22b) having a methoxy substituent, said intermediates being represented by formula (22b-1), may be prepared as described by Brown et al. J. Med. Chem. 1989, 32, 807- 826, or as outlined in the following scheme.

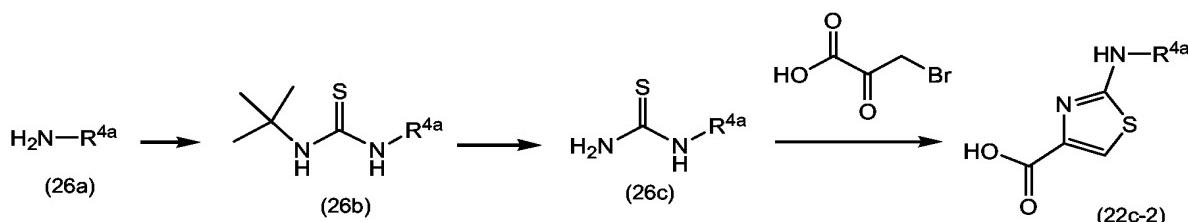


Starting materials ethyl acetylacetate and ethoxymethylene malononitrile, which are commercially available, are reacted in the presence of a suitable base, such as sodium ethoxide, and a solvent, such as ethanol and the like. This reaction affords intermediate (25a). The latter is hydrolyzed, e.g. with a base such as an alkali metal hydroxide, e.g. NaOH or LiOH, in a suitable solvent such as ethanol/water to produce (25b).

Decarboxylation of intermediate (25b) to intermediate (25c) is performed at increased temperature, preferably in the presence of a basic solvent such as quinoline.

Methylation of intermediate (25c), in particular with a methylating agent such as MeI in the presence of a suitable base (e.g. K₂CO₃) in a suitable solvent (such as DMF and the like) yields (25d). The latter is reacted with a Grignard reagent such as MeMgBr in the presence of a suitable solvent (e.g. THF), followed by hydrolysis, for instance with aqueous HCl, affording intermediate (22b-1).

The synthesis of further carboxylic acids (22c), in particular of substituted amino thiazole carboxylic acids (22c-2) is illustrated herebelow:



Thiourea (26c) with various substituents R^{4a} , which in particular are C_{1-6} alkyl, can be formed by reaction of the appropriate amine (26a) with *tert*-butylisothiocyanate in the presence of a base like diisopropylethylamine in a solvent like dichloromethane followed by removal of the *tert*-butyl group under acidic conditions. Subsequent condensation of thiourea derivative (26c) with 3-bromopyruvic acid provides the thiazole carboxylic acid (22c-2).

Compounds of the present invention or building blocks P2 wherein a heterocyclic R^1 group is attached via a ring nitrogen directly to the pyrrolidine, cyclopentane or cyclopentene ring, i.e. L is a direct bond in general formula (I), can be prepared for example by using a replacement reaction wherein a suitable leaving group on the pyrrolidine ring is replaced by a nitrogen-containing cyclic group. This can be done at the building block stage or after assembling and/or cyclizing the building blocks. In one procedure the pyrrolidine derivative (4a), (XI), (XVI), (XXV) or any intermediate having an L^3 group that is hydroxy, is reacted with a leaving group introducing reagent, such as with a halogenating agent, for example phosphoryl chloride or the like, or with an arylsulfonyl chloride, e.g. with tosyl chloride. The thus formed intermediate is then reacted with a heterocycle having a ring nitrogen substituted with hydrogen (i.e. N-H).

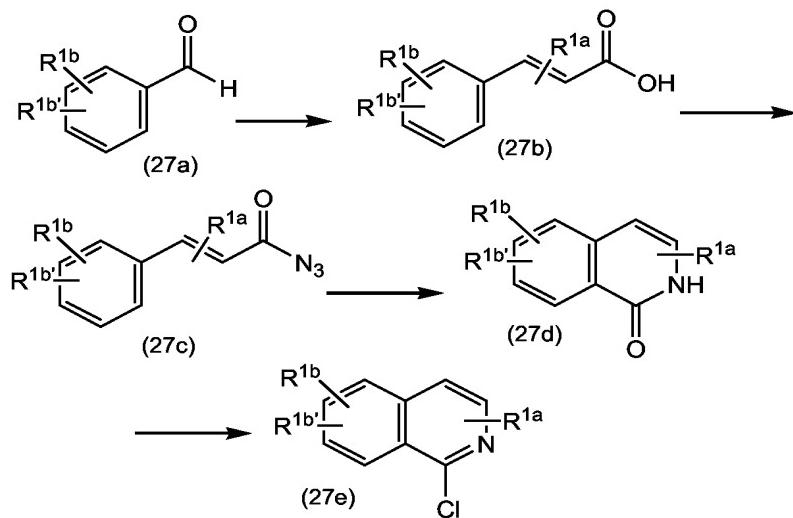
Compounds of formula (I) wherein L is a direct bond and R^1 is a ring system connected to the pyrrolidine moiety via a carbon atom can be prepared by building up the ring starting from the hydroxy compounds. This can either be done at the building block stage or after assembling and/or cyclizing the building blocks. For example, the hydroxy function may be converted into a leaving group which in turn is substituted by a cyano group. This cyano group in turn can be further converted into the desired heterocycles. For example, compounds wherein a tetrazole derivative is attached through a carbon atom of the tetrazolic ring are conveniently prepared by building up the tetrazole moiety directly onto the pyrrolidine-ring precursor. This can be achieved for instance by condensing the thus introduced cyano group followed by reaction with an azide reagent like sodium azide. Triazole derivatives can also be built up directly onto the nitrogen-ring precursor for example by transforming the hydroxy group of the nitrogen-ring precursor into an azide group followed by a 3+2 cycloaddition reaction of the obtained azide with a suitable alkyne derivative.

Structurally diverse tetrazoles for use in the above reactions to introduce a R¹ group can be prepared by reacting commercially available nitrile compounds with sodium azide. Triazole derivatives can be prepared by reaction of an alkyne compound and trimethylsilyl azide. Useful alkyne compounds are either commercially available or they can be prepared for instance according to the Sonogashira reaction, i.e. reaction of a primary alkyne, an aryl halide and triethylamine in the presence of PdCl₂(PPh)₃ and CuI as described for example in A. Elangovan, Y.-H. Wang, T.-I. Ho, Org. Lett., 2003, 5, 1841-1844. The heterocyclic substituent can also be modified when attached to the P2 building block either before or after coupling of the P2 building block to the other building blocks.

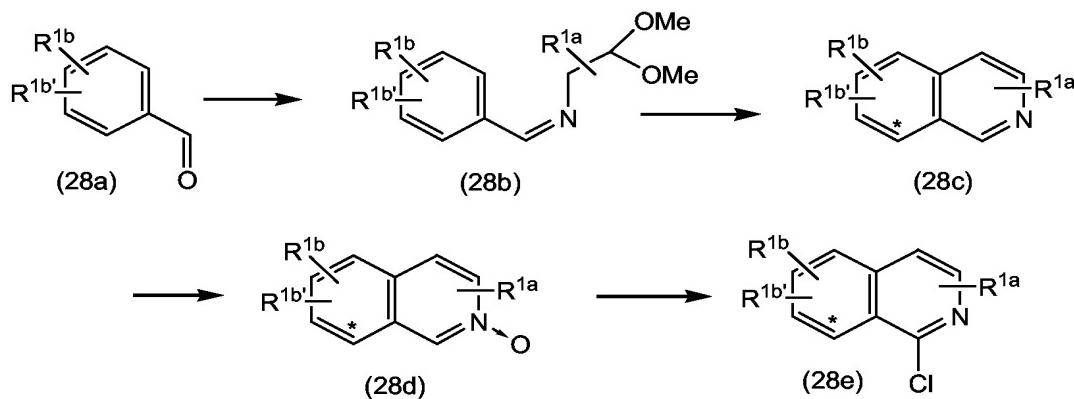
Further alternatives for the preparation of compounds wherein L is a bond and R¹ is an optionally substituted heterocycle can be found for example in WO 2004/072243.

Building blocks P2 wherein L is a urethane group (L is -O-C(=O)-NR^{4a}-) can be prepared by reacting (4a), (6a) or their cyclopentane analogues, e.g. (5a), with phosgene thus providing the corresponding chloroformate which upon reaction with an amine, R¹-NH₂, or H-NR¹R^{4a}, provides carbamates i.e. L is -OC(=O)NH- or -OC(=O)NR^{4a}-; whereas reaction of alcohols (4a), (6a), or (5a) with an acylating agent, like an acid anhydride or acid halide for instance an acid chloride (R¹-C(=O)Cl), provide esters, i.e. L is -O-C(=O)-. The reactions of the chloroformate with the amine preferably and the acid chloride with the alcohol (4a), (6a), or (5a) preferably are conducted in the presence of a base such as an alkali metal carbonate or hydrogen carbonate, e.g. sodium hydrogen carbonate, or a trialkylamine, e.g. triethylamine.

Intermediates (4b), which are isoquinoline derivatives, can be prepared using art-known procedures. For example, US 2005/0143316 provides diverse methods for the synthesis of isoquinolines as R¹-OH or R¹-LG intermediates. Methodology for the synthesis of such isoquinolines has been described by N. Briet et al., Tetrahedron, 2002, 5761 and is shown below, wherein R^{1a}, R^{1b} and R^{1b'} are substituents on the isoquinoline moiety having the meanings defined herein for the substituents on the R¹-group.



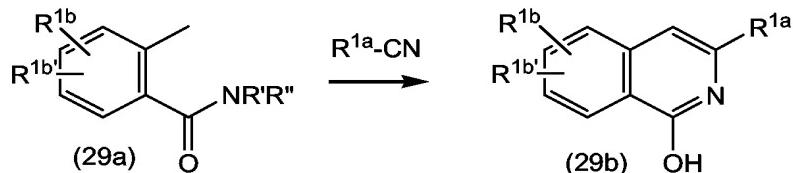
Cinnamic acid derivatives (27b) are converted to 1-chloroisoquinolines in a three-step process. The resulting chloroisoquinolines can be subsequently coupled to hydroxypyrrolidine, hydroxycyclopentane or hydroxycyclopentene derivatives as described herein. In a first step, the carboxyl group in cinnamic acid (27b) is activated, for example by treatment with a C₁₋₆alkyl (in particular methyl or ethyl) chloroformate in the presence of a base. The resulting mixed anhydride is then treated with sodium azide yielding the acyl azide (27c). Several other methods are available for the formation of acylazides from carboxylic acids, for example the carboxylic acid can be treated with diphenylphosphorylazide (DPPA) in an aprotic solvent such as methylene chloride, in the presence of a base. In a next step the acyl azide (27c) is converted to the corresponding isoquinolone (27d) by heating the acylazide, in a high boiling solvent such as diphenylether. The starting cinnamic acid derivatives are commercially available or can be obtained from the corresponding benzaldehydes (27a) by direct condensation with malonic acids or derivatives thereof, or by employing a Wittig reaction. The intermediate isoquinolones (27d) can be converted to the corresponding 1-chloro-isoquinolines by treatment with a halogenating agent such as phosphorous oxychloride.



R^1 -groups which are isoquinolines can also be prepared following procedures as described in K. Hirao, R. Tsuchiya, Y. Yano, H. Tsue, *Heterocycles* 42(1) 1996, 415-422.

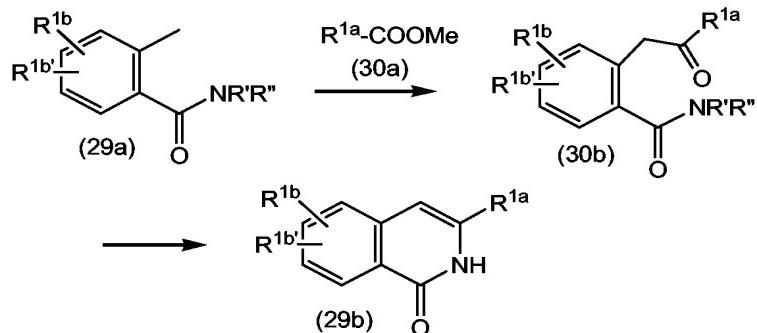
An alternative method for the synthesis of the isoquinoline ring system is the Pomeranz-Fritsch procedure. This method begins with the conversion of a benzaldehyde derivative (28a) to a functionalized imine (28b) which then is converted to an isoquinoline ring system by treatment with acid at elevated temperature. This method is particularly useful for preparing isoquinoline intermediates that are substituted at the C8 position indicated by the asterisk. The intermediate isoquinolines (28c) can be converted to the corresponding 1-chloroquinolines (28e) in a two step process. The first step comprises the formation of an isoquinoline N-oxide (28d) by treatment of isoquinoline (28c) with a peroxide such as meta-chloroperbenzoic acid in an appropriate solvent such as dichloromethane. Intermediate (28d) is converted to the corresponding 1-chloroisoquinoline by treatment with a halogenating agent such as phosphorous oxychloride.

Another method for the synthesis of the isoquinoline ring system is shown in the scheme below.



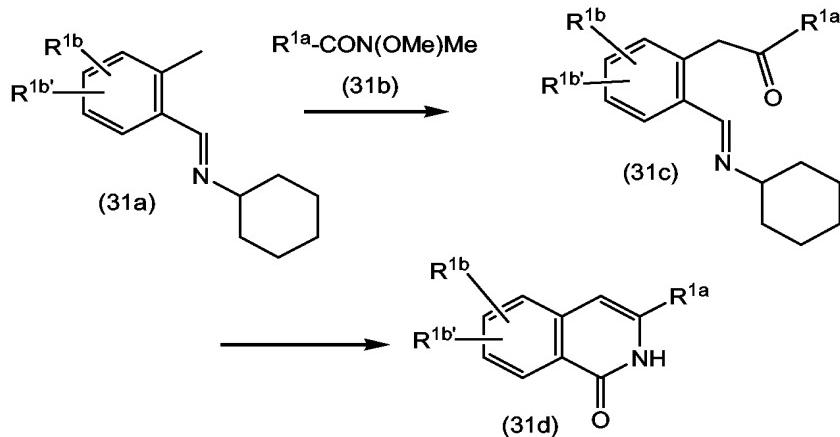
In this process the anion form of ortho-alkylbenzamide derivative (29a) is obtained by treatment with a strong base such as *tert*-butyl lithium in a solvent such as THF and is subsequently condensed with a nitrile derivative, yielding isoquinoline (29b). The latter can be converted to the corresponding 1-chloroisoquinoline by the methods described above. R' and R'' in (29a) are alkyl groups, in particular C_{1-4} alkyl groups, e.g. methyl or ethyl.

The following scheme shows an additional method for the synthesis of isoquinolines.



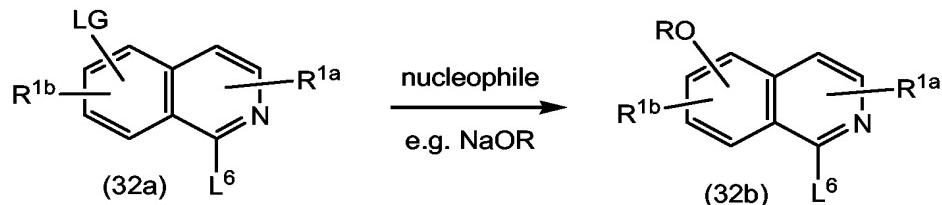
Intermediate (29a) is deprotonated using a strong base as described above. R' and R'' are as specified above. The resulting intermediate anion is condensed with an ester (30a), obtaining ketone intermediate (30b). In a subsequent reaction the latter intermediate (30b) is reacted with ammonia or an ammonium salt, e.g. ammonium acetate, at elevated temperature, resulting in the formation of isoquinolone (29b).

Yet an additional method for the preparation of isoquinolines is illustrated in the following reaction scheme.



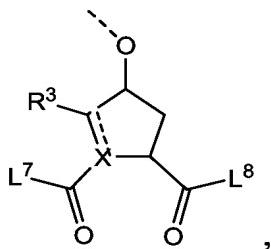
In the first step of this process an ortho-alkylarylimine derivative (31a) is subjected to deprotonation conditions (e.g. sec-butyl lithium, THF) and the resulting anion is condensed with an activated carboxylic acid derivative such as a Weinreb amide (31b). The resulting keto imine (31c) is converted to the isoquinoline (31d) by condensation with ammonium acetate at elevated temperatures. The thus obtained isoquinolines can be converted to the corresponding 1-chloroisoquinolines by the methods described herein.

The isoquinolines described herein, either as such or incorporated onto the hydroxy-pyrrolidine, hydroxycyclopentane or hydroxycyclopentane moieties in the compounds of formula (I) or in any of the intermediates mentioned herein, can be further functionalized. An example of such functionalization is illustrated herebelow.



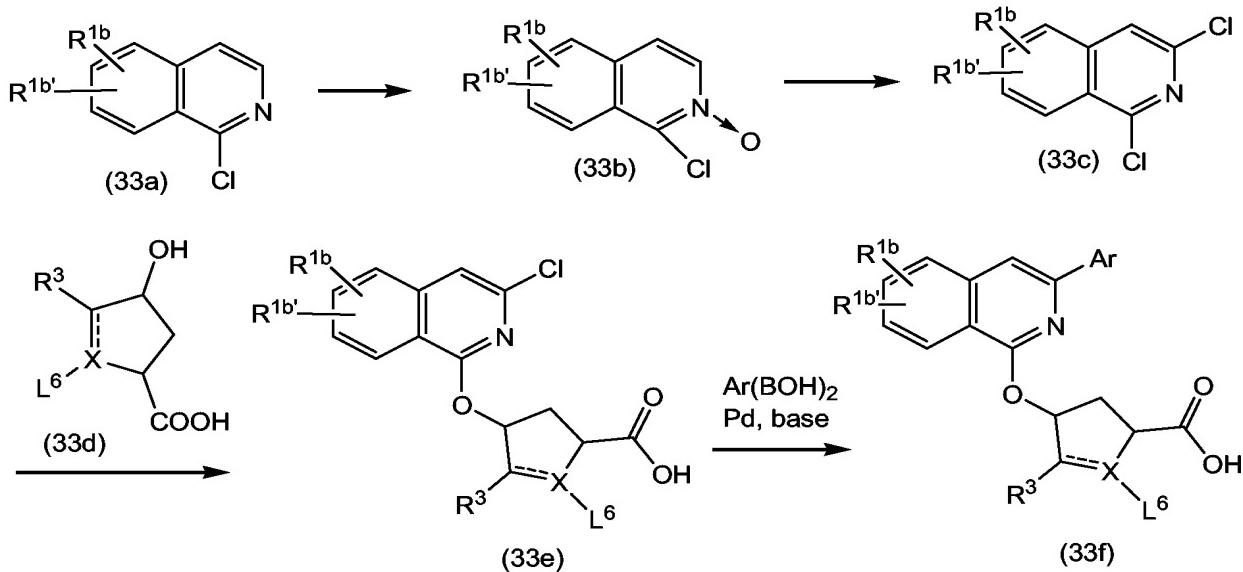
The above scheme shows the conversion of a 1-chloro-6-fluoro-isoquinoline to the corresponding 1-chloro-6-C₁-₆alkoxy-isoquinoline moiety (32b), by treatment of (32a)

with a sodium or potassium alkoxide in an alcohol solvent from which the alkoxide is derived. L⁶ in the above scheme represents halo or a group



R represents C₁₋₆alkyl and LG is a leaving group. In one embodiment LG is fluoro. L⁷ and L⁸ represent various substituents that can be linked at these positions of the P2 moiety, in particular groups such as OL⁵, or L⁸ may be a P1 group and L⁷ a P3 group, or L⁷ and L⁸ taken together may form the remainder of the macrocyclic ring system of the compounds of formula (I).

The following scheme provides an example for the modification of isoquinolines by Suzuki reactions. These couplings can be employed to functionalize an isoquinoline at each position of the ring system provided said ring is suitably activated or functionalized, as for example with chloro.



This sequence begins with 1-chloroisouinoline (33a) which upon treatment with a peroxide such as metachloroperbenzoic acid is converted to the corresponding N-oxide (33b). The latter intermediate is converted to the corresponding 1,3-dichloroisouinoline (33c) by treatment with a halogenating agent, e.g. phosphorous oxychloride. Intermediate (33c) can be coupled with an intermediate (33d), wherein L⁶

is a group PG where X is N, or L⁶ is a group -COOPG² where X is C, using methods described herein for introducing -L-R¹-groups, to provide intermediate (33e).

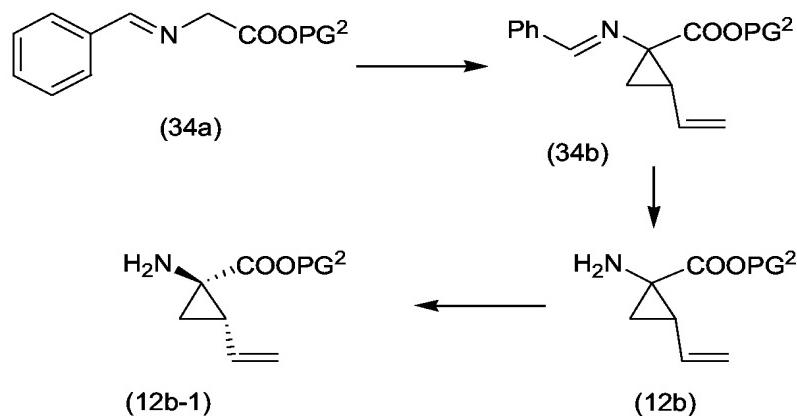
Intermediate (33e) is derivatized using a Suzuki coupling with an aryl boronic acid, in the presence of a palladium catalyst and a base, in a solvent such as THF, toluene or a dipolar aprotic solvent such as DMF, to provide the C3-arylisoquinoline intermediate (15f). Heteroarylboronic acids can also be employed in this coupling process to provide C3-heteroarylisoquinolines.

Suzuki couplings of isoquinolines systems with aryl or heteroaryl groups can also be employed at a later synthesis stage in the preparation of compounds of formula (I). The isoquinoline ring systems can also be functionalized by employing other palladium catalyzed reactions, such as the Heck, Sonogashira or Stille couplings as illustrated for example in US 2005/1043316.

Synthesis of P1 building blocks

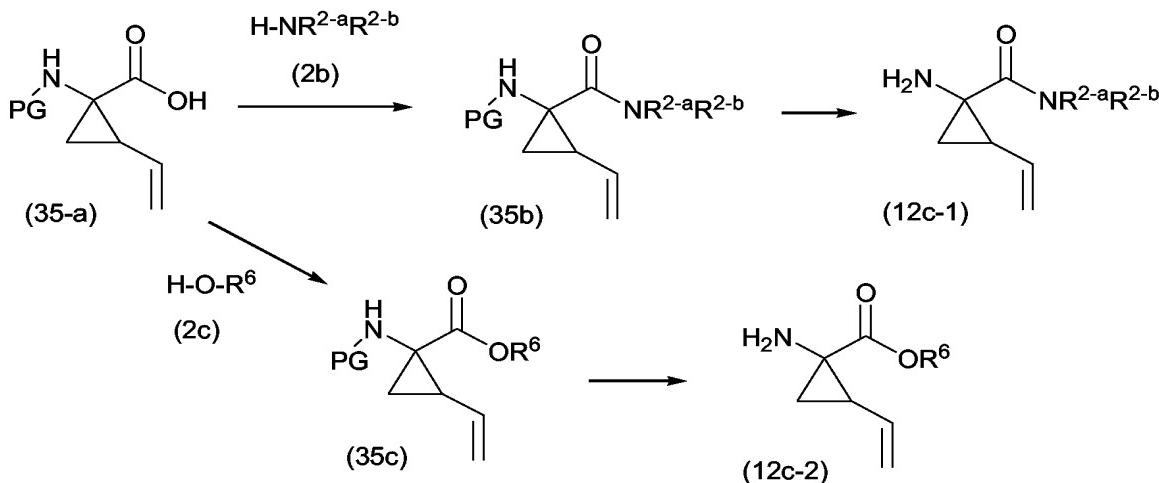
The cyclopropane amino acid used in the preparation of the P1 fragment is commercially available or can be prepared using art-known procedures.

The amino-vinyl-cyclopropyl ethyl ester (12b) may be obtained according to the procedure described in WO 00/09543 or as illustrated in the following scheme, wherein PG² is a carboxyl protecting group as specified above:



Treatment of commercially available or easily obtainable imine (34a) with 1,4-dihalobutene in presence of a base produces (34b), which after hydrolysis yields cyclopropyl amino acid (12b), having the allyl substituent *syn* to the carboxyl group. Resolution of the enantiomeric mixture (12b) results in (12b-1). The resolution is performed using art-known procedures such as enzymatic separation; crystallization with a chiral acid; or chemical derivatization; or by chiral column chromatography. Intermediates (12b) or (12b-1) may be coupled to the appropriate proline derivatives as described above.

Introduction of a N-protecting group PG and removal of PG² results in cyclopropyl amino acids (35s) which are converted to the amides (12c-1) or esters (12c-2), which are subgroups of the intermediates (12c), as outlined in the following reaction scheme, wherein R^{2-a}, R^{2-b} and PG are as specified above.



The reaction of (35a) with amine (2b) is an amide forming procedure. The similar reaction with (2c) is an ester forming reaction. Both can be performed following the procedures described above. This reaction yields intermediates (35b) or (35c) from which the amino protecting group is removed by standard methods such as those described above. This in turn results in the desired intermediate (12c-1). Starting materials (35a) may be prepared from the above mentioned intermediates (12b) by first introducing a N-protecting group PG and subsequent removal of the group PG².

In one embodiment the reaction of (35a) with (2b) is done by treatment of the amino acid with a coupling agent, for example N,N'-carbonyl-diimidazole (CDI) or the like, in a solvent like THF followed by reaction with (2b) in the presence of a base such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Alternatively the amino acid can be treated with (2b) in the presence of a base like diisopropylethylamine followed by treatment with a coupling agent such as benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate (commercially available as PyBOP®) to effect the introduction of the sulfonamide group.

Intermediates (12c-1) or (12c-2) in turn may be coupled to the appropriate proline derivatives as described above.

P1 building blocks for the preparation of compounds according to general formula (I) wherein R² is -OR⁵ or -NR^{4a}R^{4b} can be prepared by reacting amino acid (35a) with the

appropriate alcohol or amine respectively under standard conditions for ester or amide formation.

Synthesis of the P3 building blocks

The P3 building blocks are available commercially or can be generated according to methodologies known to the skilled in the art.

Coupling of the appropriate P3 building block to P2-P or P2 moieties have been described above. Coupling of a P3 building block to P1 or P1-P2 moieties can be achieved via formation of a double bond, such as a Wittig synthesis or preferably by an olefin metathesis reaction as described herein above.

Compounds of formula (I) may be converted into each other following art-known functional group transformation reactions. For example, amino groups may be N-alkylated, nitrogroups reduced to aminogroups, a halo atom may be exchanged for another halo.

The compounds of formula (I) may be converted to the corresponding *N*-oxide forms following art-known procedures for converting a trivalent nitrogen into its *N*-oxide form. Said *N*-oxidation reaction may generally be carried out by reacting the starting material of formula (I) with an appropriate organic or inorganic peroxide. Appropriate inorganic peroxides comprise, for example, hydrogen peroxide, alkali metal or earth alkaline metal peroxides, e.g. sodium peroxide, potassium peroxide; appropriate organic peroxides may comprise peroxy acids such as, for example, benzenecarbo-peroxyic acid or halo substituted benzenecarboperoxyic acid, e.g. 3-chlorobenzene-carboperoxyic acid, peroxyoalkanoic acids, e.g. peroxyacetic acid, alkylhydroperoxides, e.g. *tert*-butyl hydro-peroxide. Suitable solvents are, for example, water, lower alcohols, e.g. ethanol and the like, hydrocarbons, e.g. toluene, ketones, e.g. 2-butanone, halogenated hydrocarbons, e.g. dichloromethane, and mixtures of such solvents.

Pure stereochemically isomeric forms of the compounds of formula (I) may be obtained by the application of art-known procedures. Diastereomers may be separated by physical methods such as selective crystallization and chromatographic techniques, e.g., counter-current distribution, liquid chromatography and the like.

The compounds of formula (I) may be obtained as racemic mixtures of enantiomers which can be separated from one another following art-known resolution procedures. The racemic compounds of formula (I), which are sufficiently basic or acidic may be converted into the corresponding diastereomeric salt forms by reaction with a suitable

chiral acid, respectively chiral base. Said diastereomeric salt forms are subsequently separated, for example, by selective or fractional crystallization and the enantiomers are liberated therefrom by alkali or acid. An alternative manner of separating the enantiomeric forms of the compounds of formula (I) involves liquid chromatography, in particular liquid chromatography using a chiral stationary phase. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically. Preferably if a specific stereoisomer is desired, said compound may be synthesized by stereospecific methods of preparation. These methods may advantageously employ enantiomerically pure starting materials.

In a further aspect, the present invention concerns a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula (I) as specified herein, or a compound of any of the subgroups of compounds of formula (I) as specified herein, and a pharmaceutically acceptable carrier. A therapeutically effective amount in this context is an amount sufficient to prophylactically act against, to stabilize or to reduce viral infection, and in particular HCV viral infection, in infected subjects or subjects being at risk of being infected. In still a further aspect, this invention relates to a process of preparing a pharmaceutical composition as specified herein, which comprises intimately mixing a pharmaceutically acceptable carrier with a therapeutically effective amount of a compound of formula (I), as specified herein, or of a compound of any of the subgroups of compounds of formula (I) as specified herein.

Therefore, the compounds of the present invention or any subgroup thereof may be formulated into various pharmaceutical forms for administration purposes. As appropriate compositions there may be cited all compositions usually employed for systemically administering drugs. To prepare the pharmaceutical compositions of this invention, an effective amount of the particular compound, optionally in addition salt form or metal complex, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirable in unitary dosage form suitable, particularly, for administration orally, rectally, percutaneously, or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs, emulsions and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules, and tablets.

Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit forms, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not introduce a significant deleterious effect on the skin.

The compounds of the present invention may also be administered via oral inhalation or insufflation by means of methods and formulations employed in the art for administration via this way. Thus, in general the compounds of the present invention may be administered to the lungs in the form of a solution, a suspension or a dry powder, a solution being preferred. Any system developed for the delivery of solutions, suspensions or dry powders via oral inhalation or insufflation are suitable for the administration of the present compounds.

Thus, the present invention also provides a pharmaceutical composition adapted for administration by inhalation or insufflation through the mouth comprising a compound of formula (I) and a pharmaceutically acceptable carrier. Preferably, the compounds of the present invention are administered via inhalation of a solution in nebulized or aerosolized doses.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in unit dosage form for ease of administration and uniformity of dosage. Unit dosage form as used herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such unit dosage forms are tablets (including scored or coated tablets), capsules, pills, suppositories, powder packets, wafers, injectable solutions or suspensions and the like, and segregated multiples thereof.

The compounds of formula (I) show antiviral properties. Viral infections and their associated diseases treatable using the compounds and methods of the present invention include those infections brought on by HCV and other pathogenic flaviviruses such as Yellow fever, Dengue fever (types 1-4), St. Louis encephalitis, Japanese encephalitis, Murray valley encephalitis, West Nile virus and Kunjin virus. The diseases associated with HCV include progressive liver fibrosis, inflammation and necrosis leading to cirrhosis, end-stage liver disease, and HCC; and for the other pathogenic flaviruses the diseases include yellow fever, dengue fever, hemorrhagic fever and encephalitis. A number of the compounds of this invention moreover are active against mutated strains of HCV. Additionally, many of the compounds of this invention show a favorable pharmacokinetic profile and have attractive properties in terms of bioavailability, including an acceptable half-life, AUC (area under the curve) and peak values and lacking unfavourable phenomena such as insufficient quick onset and tissue retention.

The *in vitro* antiviral activity against HCV of the compounds of formula (I) was tested in a cellular HCV replicon system based on Lohmann et al. (1999) Science 285:110-113, with the further modifications described by Krieger et al. (2001) Journal of Virology 75: 4614-4624, which is further exemplified in the examples section. This model, while not a complete infection model for HCV, is widely accepted as the most robust and efficient model of autonomous HCV RNA replication currently available. Compounds exhibiting anti-HCV activity in this cellular model are considered as candidates for further development in the treatment of HCV infections in mammals. It will be appreciated that it is important to distinguish between compounds that specifically interfere with HCV functions from those that exert cytotoxic or cytostatic effects in the HCV replicon model, and as a consequence cause a decrease in HCV RNA or linked reporter enzyme concentration. Assays are known in the field for the evaluation of cellular cytotoxicity based for example on the activity of mitochondrial enzymes using fluorogenic redox dyes such as resazurin. Furthermore, cellular counter screens exist for the evaluation of non-selective inhibition of linked reporter gene activity, such as firefly luciferase. Appropriate cell types can be equipped by stable transfection with a luciferase reporter gene whose expression is dependent on a constitutively active gene promoter, and such cells can be used as a counter-screen to eliminate non-selective inhibitors.

Due to their antiviral properties, particularly their anti-HCV properties, the compounds of formula (I) or any subgroup thereof, their prodrugs, *N*-oxides, addition salts, quaternary amines, metal complexes and stereochemically isomeric forms, are useful in the treatment of individuals experiencing a viral infection, particularly a HCV infection, and for the prophylaxis of these infections. In general, the compounds of the

present invention may be useful in the treatment of warm-blooded animals infected with viruses, in particular flaviviruses such as HCV.

The compounds of the present invention or any subgroup thereof may therefore be used as medicines. Said use as a medicine or method of treatment comprises the systemic administration to viral infected subjects or to subjects susceptible to viral infections of an amount effective to combat the conditions associated with the viral infection, in particular the HCV infection.

The present invention also relates to the use of the present compounds or any subgroup thereof in the manufacture of a medicament for the treatment or the prevention of viral infections, particularly HCV infection.

The present invention furthermore relates to a method of treating a warm-blooded animal infected by a virus, or being at risk of infection by a virus, in particular by HCV, said method comprising the administration of an anti-virally effective amount of a compound of formula (I), as specified herein, or of a compound of any of the subgroups of compounds of formula (I), as specified herein.

Also, the combination of previously known anti-HCV compound, such as, for instance, interferon- α (IFN- α), pegylated interferon- α and/or ribavirin, and a compound of formula (I) can be used as a medicine in a combination therapy. The term “combination therapy” relates to a product containing mandatory (a) a compound of formula (I), and (b) optionally another anti-HCV compound, as a combined preparation for simultaneous, separate or sequential use in treatment of HCV infections, in particular, in the treatment of infections with HCV.

Anti-HCV compounds encompass agents selected from an HCV polymerase inhibitor, an HCV protease inhibitor, an inhibitor of another target in the HCV life cycle, and immunomodulatory agent, an antiviral agent, and combinations thereof.

HCV polymerase inhibitors include, but are not limited to, NM283 (valopicitabine), R803, JTK-109, JTK-003, HCV-371, HCV-086, HCV-796 and R-1479.

Inhibitors of HCV proteases (NS2-NS3 inhibitors and NS3-NS4A inhibitors) include, but are not limited to, the compounds of WO02/18369 (see, e.g., page 273, lines 9-22 and page 274, line 4 to page 276, line 11); BILN-2061, VX-950, GS-9132 (ACH-806), SCH-503034, and SCH-6. Further agents that can be used are those disclosed in WO-98/17679, WO-00/056331 (Vertex); WO 98/22496 (Roche); WO 99/07734,

(Boehringer Ingelheim), WO 2005/073216, WO2005073195 (Medivir) and structurally similar agents.

Inhibitors of other targets in the HCV life cycle, including NS3 helicase; metalloprotease inhibitors; antisense oligonucleotide inhibitors, such as ISIS-14803, AVI-4065 and the like; siRNA's such as SIRPLEX-140-N and the like; vector-encoded short hairpin RNA (shRNA); DNAzymes; HCV specific ribozymes such as heptazyme, RPI.13919 and the like; entry inhibitors such as HepeX-C, HuMax-HepC and the like; alpha glucosidase inhibitors such as celgosivir, UT-231B and the like; KPE-02003002; and BIVN 401.

Immunomodulatory agents include, but are not limited to; natural and recombinant interferon isoform compounds, including α -interferon, β -interferon, γ -interferon, ω -interferon and the like, such as Intron A®, Roferon-A®, Canferon-A300®, Advaferon®, Infergen®, Humoferon®, Sumiferon MP®, Alfaferone®, IFN-beta®, Feron® and the like; polyethylene glycol derivatized (pegylated) interferon compounds, such as PEG interferon- α -2a (Pegasys®), PEG interferon- α -2b (PEG-Intron®), pegylated IFN- α -con1 and the like; long acting formulations and derivatizations of interferon compounds such as the albumin-fused interferon albuferon α and the like; compounds that stimulate the synthesis of interferon in cells, such as resiquimod and the like; interleukins; compounds that enhance the development of type 1 helper T cell response, such as SCV-07 and the like; TOLL-like receptor agonists such as CpG-10101 (actilon), isatoribine and the like; thymosin α -1; ANA-245; ANA-246; histamine dihydrochloride; propagermanium; tetrachlorodecaoxide; ampligen; IMP-321; KRN-7000; antibodies, such as civacir, XTL-6865 and the like; and prophylactic and therapeutic vaccines such as InnoVac C, HCV E1E2/MF59 and the like.

Other antiviral agents include, but are not limited to, ribavirin, amantadine, viramidine, nitazoxanide; telbivudine; NOV-205; taribavirin; inhibitors of internal ribosome entry; broad-spectrum viral inhibitors, such as IMPDH inhibitors (e.g., compounds of US5,807,876, US6,498,178, US6,344,465, US6,054,472, WO97/40028, WO98/40381, WO00/56331, and mycophenolic acid and derivatives thereof, and including, but not limited to VX-950, merimepodib (VX-497), VX-148, and/or VX-944); or combinations of any of the above.

Thus, to combat or treat HCV infections, the compounds of formula (I) may be co-administered in combination with for instance, interferon- α (IFN- α), pegylated interferon- α and/or ribavirin, as well as therapeutics based on antibodies targeted

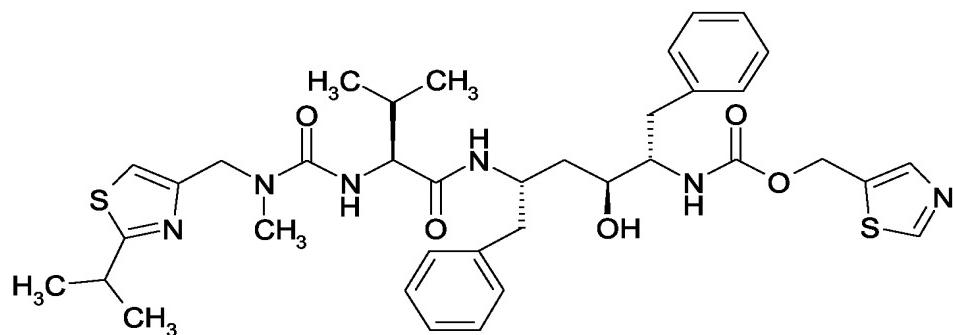
against HCV epitopes, small interfering RNA (Si RNA), ribozymes, DNAzymes, antisense RNA, small molecule antagonists of for instance NS3 protease, NS3 helicase and NS5B polymerase.

Accordingly, the present invention relates to the use of a compound of formula (I) or any subgroup thereof as defined above for the manufacture of a medicament useful for inhibiting HCV activity in a mammal infected with HCV viruses, wherein said medicament is used in a combination therapy, said combination therapy preferably comprising a compound of formula (I) and another HCV inhibitory compound, e.g. (pegylated) IFN- α and/or ribavirin.

In still another aspect there are provided combinations of a compound of formula (I) as specified herein and an anti-HIV compound. The latter preferably are those HIV inhibitors that have a positive effect on drug metabolism and/or pharmacokinetics that improve bioavailability. An example of such an HIV inhibitor is ritonavir.

As such, the present invention further provides a combination comprising (a) an HCV NS3/4a protease inhibitor of formula (I) or a pharmaceutically acceptable salt thereof; and (b) ritonavir or a pharmaceutically acceptable salt thereof.

The compound ritonavir, and pharmaceutically acceptable salts thereof, and methods for its preparation are described in WO94/14436. For preferred dosage forms of ritonavir, see US6,037, 157, and the documents cited therein: US5,484, 801, US08/402,690, and WO95/07696 and WO95/09614. Ritonavir has the following formula:



In a further embodiment, the combination comprising (a) an HCV NS3/4a protease inhibitor of formula (I) or a pharmaceutically acceptable salt thereof; and (b) ritonavir or a pharmaceutically acceptable salt thereof; further comprises an additional anti-HCV compound selected from the compounds as described herein.

In one embodiment of the present invention there is provided a process for preparing a combination as described herein, comprising the step of combining an HCV NS3/4a protease inhibitor of formula (I) or a pharmaceutically acceptable salt thereof, and ritonavir or a pharmaceutically acceptable salt thereof. An alternative embodiment of this invention provides a process wherein the combination comprises one or more additional agent as described herein.

The combinations of the present invention may be used as medicaments. Said use as a medicine or method of treatment comprises the systemic administration to HCV-infected subjects of an amount effective to combat the conditions associated with HCV and other pathogenic flavi- and pestiviruses. Consequently, the combinations of the present invention can be used in the manufacture of a medicament useful for treating, preventing or combating infection or disease associated with HCV infection in a mammal, in particular for treating conditions associated with HCV and other pathogenic flavi- and pestiviruses.

In one embodiment of the present invention there is provided a pharmaceutical composition comprising a combination according to any one of the embodiments described herein and a pharmaceutically acceptable excipient. In particular, the present invention provides a pharmaceutical composition comprising (a) a therapeutically effective amount of an HCV NS3/4a protease inhibitor of the formula (I) or a pharmaceutically acceptable salt thereof, (b) a therapeutically effective amount of ritonavir or a pharmaceutically acceptable salt thereof, and (c) a pharmaceutically acceptable excipient. Optionally, the pharmaceutical composition further comprises an additional agent selected from an HCV polymerase inhibitor, an HCV protease inhibitor, an inhibitor of another target in the HCV life cycle, and immunomodulatory agent, an antiviral agent, and combinations thereof.

The compositions may be formulated into suitable pharmaceutical dosage forms such as the dosage forms described above. Each of the active ingredients may be formulated separately and the formulations may be co-administered or one formulation containing both and if desired further active ingredients may be provided.

As used herein, the term “composition” is intended to encompass a product comprising the specified ingredients, as well as any product which results, directly or indirectly, from the combination of the specified ingredients.

In one embodiment the combinations provided herein may also be formulated as a combined preparation for simultaneous, separate or sequential use in HIV therapy. In

such a case, the compound of general formula (I) or any subgroup thereof, is formulated in a pharmaceutical composition containing other pharmaceutically acceptable excipients, and ritonavir is formulated separately in a pharmaceutical composition containing other pharmaceutically acceptable excipients. Conveniently, these two separate pharmaceutical compositions can be part of a kit for simultaneous, separate or sequential use.

Thus, the individual components of the combination of the present invention can be administered separately at different times during the course of therapy or concurrently in divided or single combination forms. The present invention is therefore to be understood as embracing all such regimes of simultaneous or alternating treatment and the term "administering" is to be interpreted accordingly. In a preferred embodiment, the separate dosage forms are administered about simultaneously.

In one embodiment, the combination of the present invention contains an amount of ritonavir, or a pharmaceutically acceptable salt thereof, which is sufficient to clinically improve the bioavailability of the HCV NS3/4a protease inhibitor of formula (I) relative to the bioavailability when said HCV NS3/4a protease inhibitor of formula (I) is administered alone.

In another embodiment, the combination of the present invention contains an amount of ritonavir, or a pharmaceutically acceptable salt thereof, which is sufficient to increase at least one of the pharmacokinetic variables of the HCV NS3/4a protease inhibitor of formula (I) selected from $t_{1/2}$, C_{min} , C_{max} , C_{ss} , AUC at 12 hours, or AUC at 24 hours, relative to said at least one pharmacokinetic variable when the HCV NS3/4a protease inhibitor of formula (I) is administered alone.

A further embodiment relates to a method for improving the bioavailability of a HCV NS3/4a protease inhibitor comprising administering to an individual in need of such improvement a combination as defined herein, comprising a therapeutically effective amount of each component of said combination.

In a further embodiment, the invention relates to the use of ritonavir or a pharmaceutically acceptable salt thereof, as an improver of at least one of the pharmacokinetic variables of a HCV NS3/4a protease inhibitor of formula (I) selected from $t_{1/2}$, C_{min} , C_{max} , C_{ss} , AUC at 12 hours, or AUC at 24 hours; with the proviso that said use is not practised in the human or animal body.

The term "individual" as used herein refers to an animal, preferably a mammal, most preferably a human, who has been the object of treatment, observation or experiment.

Bioavailability is defined as the fraction of administered dose reaching systemic circulation. $t_{1/2}$ represents the half life or time taken for the plasma concentration to fall to half its original value. C_{ss} is the steady state concentration, i.e. the concentration at which the rate of input of drug equals the rate of elimination. C_{min} is defined as the lowest (minimum) concentration measured during the dosing interval. C_{max} , represents the highest (maximum) concentration measured during the dosing interval. AUC is defined as the area under the plasma concentration-time curve for a defined period of time.

The combinations of this invention can be administered to humans in dosage ranges specific for each component comprised in said combinations. The components comprised in said combinations can be administered together or separately. The NS3/4a protease inhibitors of formula (I) or any subgroup thereof, and ritonavir or a pharmaceutically acceptable salt or ester thereof, may have dosage levels of the order of 0.02 to 5.0 grams-per-day.

When the HCV NS3/4a protease inhibitor of formula (I) and ritonavir are administered in combination, the weight ratio of the HCV NS3/4a protease inhibitor of formula (I) to ritonavir is suitably in the range of from about 40:1 to about 1:15, or from about 30:1 to about 1:15, or from about 15:1 to about 1:15, typically from about 10:1 to about 1:10, and more typically from about 8:1 to about 1:8. Also useful are weight ratios of the HCV NS3/4a protease inhibitors of formula (I) to ritonavir ranging from about 6:1 to about 1:6, or from about 4:1 to about 1:4, or from about 3:1 to about 1:3, or from about 2:1 to about 1:2, or from about 1.5:1 to about 1:1.5. In one aspect, the amount by weight of the HCV NS3/4a protease inhibitors of formula (I) is equal to or greater than that of ritonavir, wherein the weight ratio of the HCV NS3/4a protease inhibitor of formula (I) to ritonavir is suitably in the range of from about 1:1 to about 15:1, typically from about 1:1 to about 10:1, and more typically from about 1:1 to about 8:1. Also useful are weight ratios of the HCV NS3/4a protease inhibitor of formula (I) to ritonavir ranging from about 1:1 to about 6:1, or from about 1:1 to about 5:1, or from about 1:1 to about 4:1, or from about 3:2 to about 3:1, or from about 1:1 to about 2:1 or from about 1:1 to about 1.5:1.

The term "therapeutically effective amount" as used herein means that amount of active compound or component or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal or human that is being sought, in the

light of the present invention, by a researcher, veterinarian, medical doctor or other clinician, which includes alleviation of the symptoms of the disease being treated. Since the instant invention refers to combinations comprising two or more agents, the "therapeutically effective amount" is that amount of the agents taken together so that the combined effect elicits the desired biological or medicinal response. For example, the therapeutically effective amount of a composition comprising (a) the compound of formula (I) and (b) ritonavir, would be the amount of the compound of formula (I) and the amount of ritonavir that when taken together have a combined effect that is therapeutically effective.

In general it is contemplated that an antiviral effective daily amount would be from 0.01 mg/kg to 500 mg/kg body weight, more preferably from 0.1 mg/kg to 50 mg/kg body weight. It may be appropriate to administer the required dose as two, three, four or more sub-doses at appropriate intervals throughout the day. Said sub-doses may be formulated as unit dosage forms, for example, containing 1 to 1000 mg, and in particular 5 to 200 mg of active ingredient per unit dosage form.

The exact dosage and frequency of administration depends on the particular compound of formula (I) used, the particular condition being treated, the severity of the condition being treated, the age, weight, sex, extent of disorder and general physical condition of the particular patient as well as other medication the individual may be taking, as is well known to those skilled in the art. Furthermore, it is evident that said effective daily amount may be lowered or increased depending on the response of the treated subject and/or depending on the evaluation of the physician prescribing the compounds of the instant invention. The effective daily amount ranges mentioned hereinabove are therefore only guidelines.

According to one embodiment, the HCV NS3/4a protease inhibitor of formula (I) and ritonavir may be co-administered once or twice a day, preferably orally, wherein the amount of the compounds of formula (I) per dose is from about 1 to about 2500 mg, and the amount of ritonavir per dose is from 1 to about 2500 mg. In another embodiment, the amounts per dose for once or twice daily co-administration are from about 50 to about 1500 mg of the compound of formula (I) and from about 50 to about 1500 mg of ritonavir. In still another embodiment, the amounts per dose for once or twice daily co-administration are from about 100 to about 1000 mg of the compound of formula (I) and from about 100 to about 800 mg of ritonavir. In yet another embodiment, the amounts per dose for once or twice daily co-administration are from about 150 to about 800 mg of the compound of formula (I) and from about 100 to about 600 mg of ritonavir. In yet another embodiment, the amounts per dose for once or

twice daily co-administration are from about 200 to about 600 mg of the compound of formula (I) and from about 100 to about 400 mg of ritonavir. In yet another embodiment, the amounts per dose for once or twice daily co-administration are from about 200 to about 600 mg of the compound of formula (I) and from about 20 to about 300 mg of ritonavir. In yet another embodiment, the amounts per dose for once or twice daily co-administration are from about 100 to about 400 mg of the compound of formula (I) and from about 40 to about 100 mg of ritonavir.

Exemplary combinations of the compound of formula (I) (mg)/ritonavir (mg) for once or twice daily dosage include 50/100, 100/100, 150/100, 200/100, 250/100, 300/100, 350/100, 400/100, 450/100, 50/133, 100/133, 150/133, 200/133, 250/133, 300/133, 50/150, 100/150, 150/150, 200/150, 250/150, 50/200, 100/200, 150/200, 200/200, 250/200, 300/200, 50/300, 80/300, 150/300, 200/300, 250/300, 300/300, 200/600, 400/600, 600/600, 800/600, 1000/600, 200/666, 400/666, 600/666, 800/666, 1000/666, 1200/666, 200/800, 400/800, 600/800, 800/800, 1000/800, 1200/800, 200/1200, 400/1200, 600/1200, 800/1200, 1000/1200, and 1200/1200. Other exemplary combinations of the compound of formula (I) (mg)/ritonavir (mg) for once or twice daily dosage include 1200/400, 800/400, 600/400, 400/200, 600/200, 600/100, 500/100, 400/50, 300/50, and 200/50.

In one embodiment of the present invention there is provided an article of manufacture comprising a composition effective to treat an HCV infection or to inhibit the NS3 protease of HCV; and packaging material comprising a label which indicates that the composition can be used to treat infection by the hepatitis C virus; wherein the composition comprises a compound of the formula (I) or any subgroup thereof, or the combination as described herein.

Another embodiment of the present invention concerns a kit or container comprising a compound of the formula (I) or any subgroup thereof, or a combination according to the invention combining an HCV NS3/4a protease inhibitor of formula (I) or a pharmaceutically acceptable salt thereof, and ritonavir or a pharmaceutically acceptable salt thereof, in an amount effective for use as a standard or reagent in a test or assay for determining the ability of potential pharmaceuticals to inhibit HCV NS3/4a protease, HCV growth, or both. This aspect of the invention may find its use in pharmaceutical research programs.

The compounds and combinations of the present invention can be used in high-throughput target-analyte assays such as those for measuring the efficacy of said combination in HCV treatment.

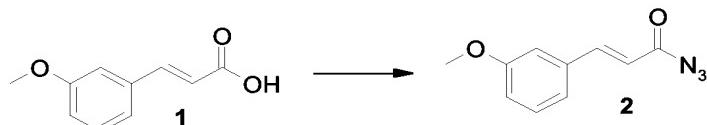
Examples

The following examples are intended to illustrate the present invention and not to limit it thereto.

Example 1

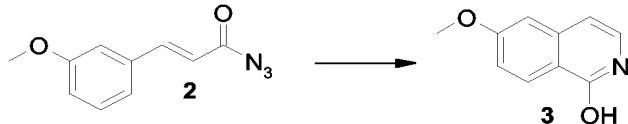
Synthesis of 1,3-dichloro-6-methoxyisoquinoline (6)

Step A



Triethylamine (80.5 mL, 578 mmol) was added at 0°C under nitrogen to a suspension of 3-methoxycinnamic acid 1 (49.90 g, 280 mmol) in acetone (225 mL). After 10 min at 0°C, ethylchloroformate (46.50 g, 429 mmol) was added dropwise while the temperature was maintained at 0°C. After 1 h at 0°C, a solution of sodium azide (27.56 g, 424 mmol) in water (200 mL) was slowly added, then the reaction mixture was allowed to warm up to RT. After 16 h, the reaction mixture was poured into water (500 mL) and the acetone was evaporated. The residue was extracted with toluene to give a solution of 2, which was used as such in the next step.

Step B



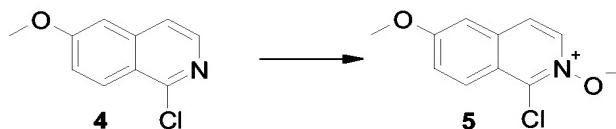
The toluene solution from the previous step was added dropwise to a heated solution of diphenylmethane (340 mL) and tributylamine (150 mL) at 190°C. The toluene was instantly distilled off via a Dean-stark. After complete addition, the reaction temperature was raised to 210°C for 2 h. After cooling, the precipitated product was collected by filtration, washed with heptane to give 49.1 g (29%) of the target product 3 as a white powder: $m/z = 176$ ($M+H$)⁺; ¹H-NMR ($CDCl_3$): 8.33 (d, $J = 8.9$ Hz, 1H), 7.13 (d, $J = 7.15$ Hz, 1H), 7.07 (dd, $J = 8.9$ Hz, 2.5 Hz 1H), 6.90 (d, $J = 2.5$ Hz, 1H), 6.48 (d, $J = 7.15$ Hz, 1H), 3.98 (s, 3H).

Step C



The phosphorus oxychloride (25 mL) was slowly added to **3** (10.00 g, 57 mmol) and this mixture was heated at gentle reflux for 3 h. After completion of the reaction, the phosphorus oxychloride was evaporated. The residue was poured into ice-cold water (40 mL) and the pH was adjusted to 10 with a solution of NaOH in water (50 W/W%). The mixture was extracted with CHCl₃, washed with brine, dried (Na₂SO₄), filtered and evaporated. The residue was purified by column chromatography (CH₂Cl₂), to give 8.42 g (76%) of the target product **4** as a yellow solid: *m/z* = 194 (M+H)⁺; ¹H-NMR (CDCl₃): 8.21 (d, *J* = 9.3 Hz, 1H); 8.18 (d, *J* = 5.7 Hz, 1H); 7.47 (d, *J* = 5.6 Hz, 1H); 7.28 (dd, *J* = 9.3 Hz, 2.5 Hz, 1H); 7.06 (d, *J* = 2.5 Hz, 1H), 3.98 (s, 3H).

Step D

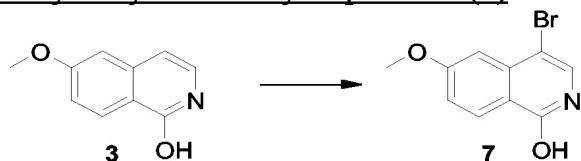


Metachloroperbenzoic acid (6.41 g, 28.6 mmol) was added in small portions at 0°C to a solution of **4** (2.70 g, 13.9 mmol) in CH₂Cl₂ (10 mL). After 30 min at 0°C, the reaction mixture was warmed up to room temperature for 12h. Then, the reaction mixture was partitioned between 1N NaOH and CH₂Cl₂ and successively washed with NaOH 1N and brine. The organic layer was dried (Na₂SO₄), filtered and evaporated to afford 1.89 g (64%) of the target product **5** as an orange solid: *m/z* = 209.9 (M+H)⁺

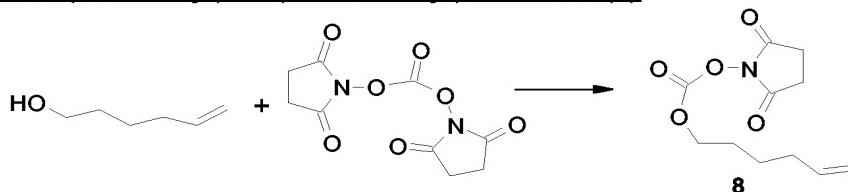
Step E



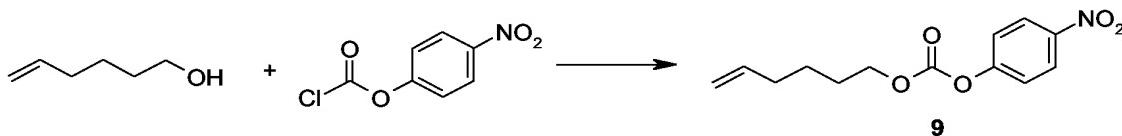
A solution of **5** (1.86 g, 8.86 mmol) in phosphorus oxychloride (18 mL) was heated at reflux for 3 h. Then, phosphorus oxychloride was evaporated in vacuo. The residue was poured into ice-cold water (50 mL) and the pH was adjusted to 10 with 50 W/W% NaOH in water. The mixture was extracted with CHCl₃, the organic layer was washed with brine, dried (Na₂SO₄), filtered and evaporated. The crude material was purified by column chromatography (CH₂Cl₂), to afford 350 mg (17%) of the target product **6** as a yellow solid: *m/z* = 227.9 (M+H)⁺; ¹H-NMR (CDCl₃): 8.16 (d, *J* = 9.3 Hz, 1H), 7.50 (s, 1H), 7.25 (dd, *J* = 9.3 Hz, 2.5 Hz, 1H). 6.98 (d, *J* = 2.5 Hz, 1H), 3.98 (s, 3H).

Synthesis of 4-bromo-1-hydroxy-6-methoxyisoquinoline (7)

N-bromosuccinimide (2.33 g, 14.3 mmol) was added to a solution of **3** (2.06 g, 11.8 mmol) in DMF (40 mL). The resulting mixture was stirred at room temperature overnight. Then, DMF was evaporated and CH₂Cl₂ was added to the residue. This suspension was heated at 45°C for 15 min. The white solid was filtered off and washed with isopropyl ether, to give 2.07 g (69 %) of the target product **7**: *m/z* = 253.7 (M+H)⁺; ¹H NMR (DMSO *d*₆): 8.14 (d, *J* = 8.8 Hz, 1H); 7.52 (s, 1H), 7.17 (dd, *J* = 8.8 Hz, 2.5 Hz, 1H), 7.11 (d, *J* = 2.4 Hz, 1H), 3.83 (s, 3H).

Synthesis of *O*-(hex-5-enyl)-*O*-(succinimidyl)carbonate (8)

A mixture of hex-5-enol (5.00 g, 49.9 mmol), disuccinimidyl carbonate (13.08 g, 51.1 mmol) and triethylamine (6.50 g, 64.2 mmol) in CH₂Cl₂ (50 mL) was stirred at RT overnight. After completion, the reaction mixture was poured on ice, the organic layer was washed with water, dried (Na₂SO₄), filtered and evaporated to afford 10.25 g (85%) of **8** as a colourless oil. *m/z* = 242 (M+H)⁺; ¹H NMR (CDCl₃): 5.82–5.73 (m, 1H), 5.07–4.96 (m, 2H), 4.33 (t, *J* = 6.3 Hz, 6.6 Hz, 2H), 2.85 (s, 4H), 2.15–2.06 (m, 2H), 1.82–1.72 (m, 2H), 1.56–1.47 (m, 2H).

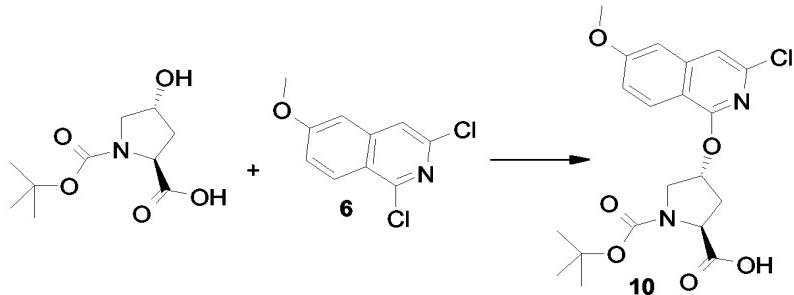
Synthesis of *O*-(hex-5-enyl)-*O*-(4-nitrophenyl) carbonate (9)

To a stirred solution of hex-5-enol (0.50 g, 5.0 mmol) in pyridine (1.2 mL, 15 mmol) and dichloromethane (20 mL) at 0 °C was added 4-nitrophenol chloroformate (1.1 g, 5.5 mmol) in one portion. After stirring for 1.5 h at room temperature, the reaction mixture was diluted with dichloromethane (10 mL) and washed successively with aqueous 10% citric acid (3 x 15 mL) and aqueous saturated sodium hydrogen carbonate (3 x 15 mL), then dried (Na₂SO₄), filtered and concentrated. Purification by flash chromatography (gradient AcOEt/hexanes, 10:90 to 15:85) gave 0.97 g (73%) of the

target product **9** as a slight yellow oil: ^1H NMR (CDCl_3 at 298 K) 8.28 (m, 2H), 7.38 (m, 2H), 5.81 (m, 1H), 5.02 (m, 2H), 4.30 (t, 2H), 2.13 (m, 2H), 1.78 (m, 2H), 1.54 (m, 2H).

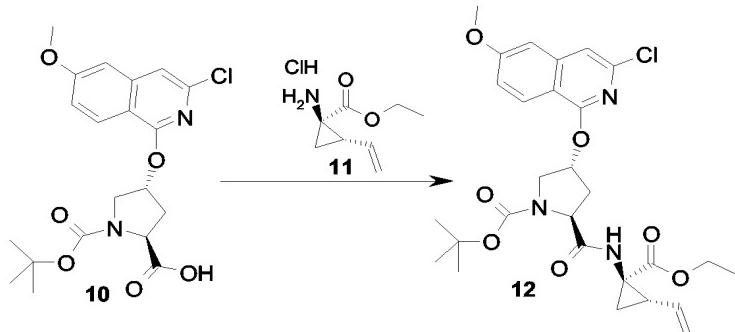
Example 2: Synthesis of 17-(3-chloro-6-methoxyisoquinolin-1-yloxy)-2,14-dioxo-3,15-diaza-13-oxatricyclo[13.3.0.0^{4,6}]octadec-7-ene-4-carboxylic acid (**16**)

Step A



To a solution of Boc-hydroxyproline (760 mg, 3.29 mmol) in DMSO (50 mL) was added potassium *tert*-butoxide (1.11 g, 9.87 mmol). The solution was stirred at the ambient temperature under nitrogen for 1 h. Then, 1,3-dichloro-6-methoxyisoquinoline **6** (750 mg, 3.29 mmol) was added. After 12 h at room temperature, the reaction mixture was quenched with ice-cold water, acidified to pH 4 with diluted HCl, extracted with EtOAc, dried (Na_2SO_4), filtered and evaporated to give 1.39 g (90 %) of the target product **10** as a solid: $m/z = 242 (\text{M}+\text{H})^+$; ^1H NMR (CDCl_3): 8.10 (d, $J = 9.3$ Hz, 1H), 7.15 (d, $J = 2.4$ Hz, 1H), 7.10 (dd, $J = 9.3$ Hz, 2.5 Hz, 1H), 6.90 (s, 1H), 5.80-5.67 (br s, 1H), 4.45 (t, $J = 7.9$ Hz, 1H), 3.95 (s, 3H); 3.80-3.90 (br s, 1H), 3.70-3.80 (m, 1H), 2.75-2.60 (m, 1H), 2.35-2.45 (m, 1H); 1.5 (s, 9H).

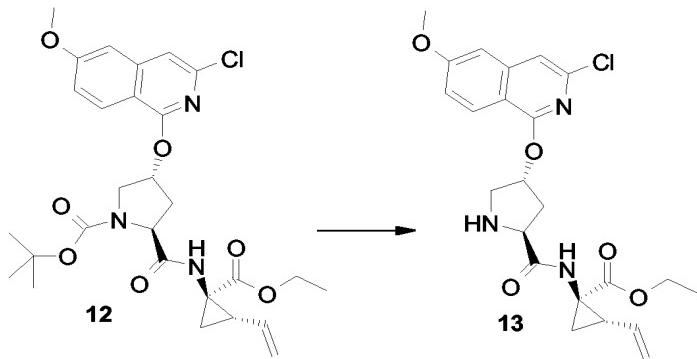
Step B



A mixture of **10** (1.25 g, 2.96 mmol), 1-amino-2-vinylcyclopropane carboxylic acid ethyl ester hydrochloride **11** (526 mg, 2.96 mmol), HATU (1.12 g, 2.96 mmol) and DIPEA (955 mg, 7.39 mmol) in DMF (50 mL) was stirred at room temperature under

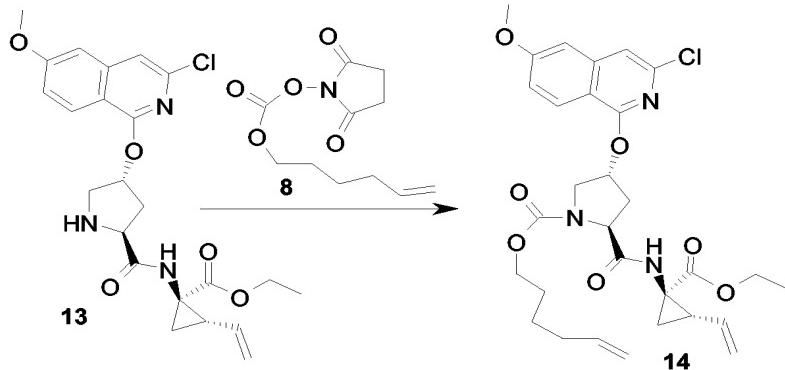
nitrogen atmosphere for 12 h. Then, the reaction mixture was diluted with dichloromethane and successively washed with aqueous NaHCO₃ and water. The organic layer was dried (MgSO₄) and concentrated. The residue was purified by column chromatography (CH₂Cl₂/MeOH, 95:5) to afford 1.5 g (90%) of the desired product **12** as a yellow foam: *m/z* = 561 (M+H)⁺; ¹H NMR (CDCl₃): 8.10 (d, *J* = 9.3 Hz, 1H), 7.50 (s, 1H), 7.25 (dd, *J* = 9.3 Hz, 2.5 Hz, 1H), 6.98 (d, *J* = 2.4 Hz, 1H), 5.80-5.67 (m, 1H), 5.29 (d, *J* = 17.1 Hz, 1H), 5.12 (d, *J* = 10.3 Hz, 1H), 4.45-4.50 (br s, 1H), 4.1-4.18 (m, 2H), 3.95 (s, 3H), 3.8-3.9 (br s, 1H), 3.7-3.8 (m, 1H), 3.25-3.35 (m, 2H), 2.35-2.45 (m, 1H), 1.50-2.20 (m, 7H), 1.50 (s, 9H).

Step C



A solution of **12** (3.0 g, 5.36 mmol) in TFA-DCM 1:2 (30 mL) was stirred at RT for 1 h. Then, the reaction mixture was co-evaporated with toluene (3.0 mL) to dryness to give the target product **13** (> 95% pure by HPLC): *m/z* = 460 (M+H)⁺.

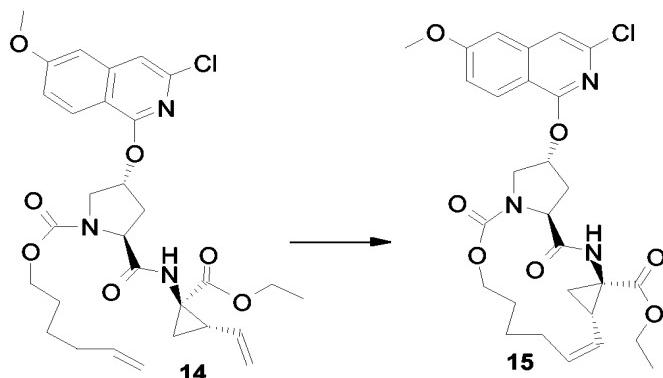
Step D



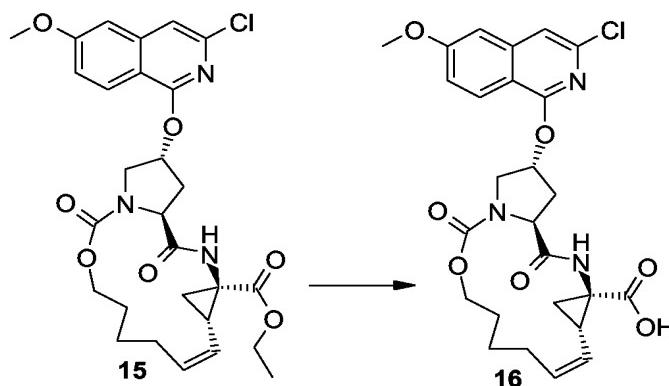
Sodium hydrogencarbonate (2.7 g, 32 mmol) was added to a solution of **13** (1.5 g, 3.26 mmol) in CH₂Cl₂ (50 mL). Then, triethylamine (681 µL, 4.89 mmol) and compound **8** (1.08 g, 4.24 mmol) were added. The reaction mixture was stirred for 12 h at room temperature, then filtrated. The reaction mixture was partitioned between water and CH₂Cl₂, dried (MgSO₄), filtered and evaporated. The residue was purified

by column chromatography on silica ($\text{CH}_2\text{Cl}_2/\text{EtOAc}$, 95:5) to give 1.73 g (90 %) of the target product **14**: $m/z = 587 (\text{M}+\text{H})^+$; $^1\text{H NMR}$ (CDCl_3): 8.10 (d, $J = 9.3$ Hz, 1H), 7.50 (s, 1H), 7.39 (s, 1H), 7.25 (dd, $J = 9.3$ Hz, 2.5 Hz, 1H), 6.98 (d, $J = 2.4$ Hz, 1H), 5.81-5.62 (m, 2H), 5.56 (t, $J = 3.8$ Hz, 1H), 5.29 (dd, $J = 1.3$ Hz, 17.2 Hz, 1H), 5.12 (dd, $J = 1.5$ Hz, 10.4 Hz, 1H), 5.00-4.86 (m, 3H), 4.35 (t, $J = 7.5$ Hz, 2H), 4.20-4.06 (m, 2H), 3.98 (s, 3H), 3.48-3.37 (m, 1H), 3.10-3.00 (m, 1H), 2.77-2.67 (m, 1H), 2.41-2.32 (m, 1H), 2.10 (dd, $J = 8.6$ Hz, 17.4 Hz, 1H), 1.98 (dd, $J = 7.1$ Hz, 14.4 Hz, 2H), 1.88 (dd, $J = 5.6$ Hz, 8.1 Hz, 1H); 1.57-1.46 (m, 3H); 1.35-1.18 (m, 5H).

Step E

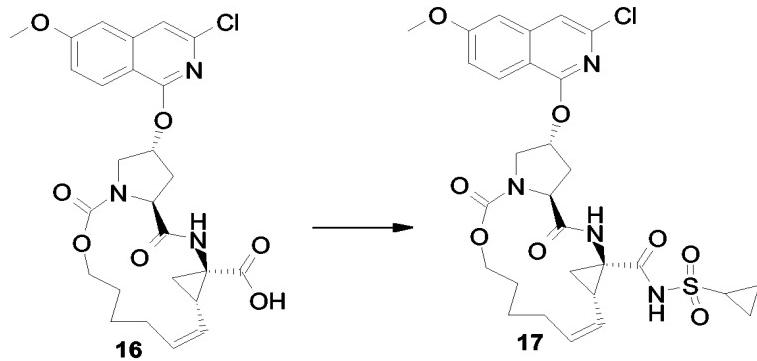


Compound **14** (1.73 g, 2.95 mmol) was dissolved in degassed dry dichloroethane (1 L), bubbled with nitrogen. Then, Hoveyda-Grubbs (1st generation) catalyst (355 mg, 20 mol %) was added and the reaction mixture was heated to 70°C for 20 h under nitrogen. The reaction mixture was cooled down to room temperature and concentrated by rotary evaporation. The resulting oil was purified by column chromatography on silica ($\text{CH}_2\text{Cl}_2/\text{EtOAc}$, 90:10) to give 530 mg (32 %) of the target compound **15** as a beige solid: $m/z = 559 (\text{M}+\text{H})^+$; $^1\text{H NMR}$ (CDCl_3): 8.10 (d, $J = 9.3$ Hz, 1H), 7.50 (s, 1H), 7.39 (s, 1H), 7.25 (dd, $J = 9.3$ Hz, 2.5 Hz, 1H), 7.2 (s, 1H), 7.1 (br s, 1H), 5.76-5.67 (m, 1H), 5.6-5.57 (bs, 1H), 5.45 (d t, $J = 1.0$ Hz, 10.0 Hz, 1H), 4.4 (t, $J = 7.8$ Hz, 2H), 4.2 (q, $J = 7.1$ Hz, 2H); 3.9 (s, 3H), 4.00-3.88 (m, 1H), 3.8-3.9 (dd, $J = 12.5$, 4.0 Hz, 1H), 2.5-2.7 (m, 3H), 2.15-2.3 (m, 2H), 1.8-2.0 (m, 3H), 1.5-1.6 (m, 1H), 1.4-1.45 (m, 1H), 1.22 (t, $J = 7.1$ Hz, 3H).

Step F

Lithium hydroxide (307 mg, 7.17 mmol) in water (3 mL) was added to a solution of **15** (200 mg, 0.358 mmol) in THF (10 mL) and methanol (2 mL). After 48 h at room temperature, the reaction mixture was diluted with water and acidified to pH 3 with a 1N solution of HCl, extracted with AcOEt, dried (Na_2SO_4), and evaporated. The solid obtained was triturated with ether to give 160 mg (84 %) of the target product **16** as a white solid $m/z = 530 (\text{M}+\text{H})^+$; ^1H NMR (CDCl_3): 8.10 (d, $J = 9.3$ Hz, 1H), 7.50 (s, 1H), 7.39 (s, 1H), 7.25 (dd, $J = 9.3$ Hz, 2.5 Hz, 1H), 7.39-7.30 (bs, 1H), 5.90-5.83 (bs, 1H), 5.71 (dd, $J = 8.0$ Hz, 17.9 Hz, 1H), 5.18 (t, $J = 10.1$ Hz, 1H), 4.79 (dd, $J = 7.3$ Hz, 9.0 Hz, 1H), 4.1 (s, 3H), 4.09-3.97 (m, 1H), 3.81-3.66 (m, 2H), 3.62 (d, $J = 11.6$ Hz, 1H), 3.19-3.05 (m, 1H), 2.59-2.22 (m, 4H), 2.01-1.90 (m, 1H), 1.89 (dd, $J = 5.8$ Hz, $J = 8.6$ Hz, 1H), 1.70 (dd, $J = 6.1$ Hz, 9.8 Hz, 1H), 1.67-1.58 (m, 2H), 1.43-1.28 (m, 2H).

Example 3: Synthesis of *N*-[17-(3-chloro-6-methoxyisoquinolin-1-yl)-2,14-dioxo-3,15-diaza-13-oxatricyclo[13.3.0.0^{4,6}]octadec-7-ene-4-carbonyl](cyclopropyl)sulfonamide (**17**)

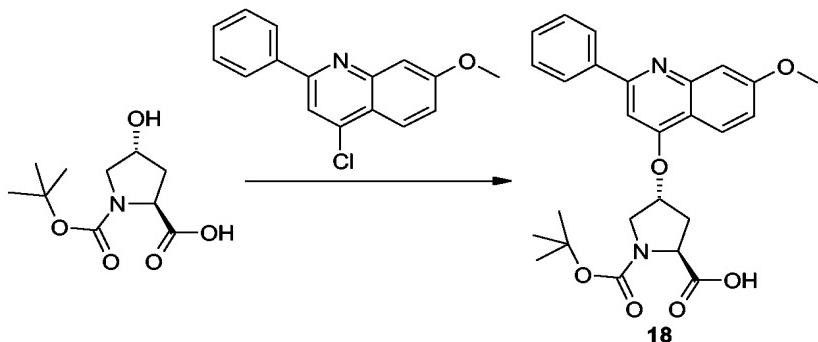


A solution of **16** (120 mg, 0.23 mmol) and carbonyldiimidazole (44 mg, 0.27 mmol) in dry THF (25 mL) was refluxed for 3h under nitrogen. Optionally, the azalactone derivative, if desired, can be isolated. Then, the reaction mixture was cooled to room temperature and cyclopropylsulfonamide (33 mg, 0.27 mmol) and DBU (52 mg, 0.34

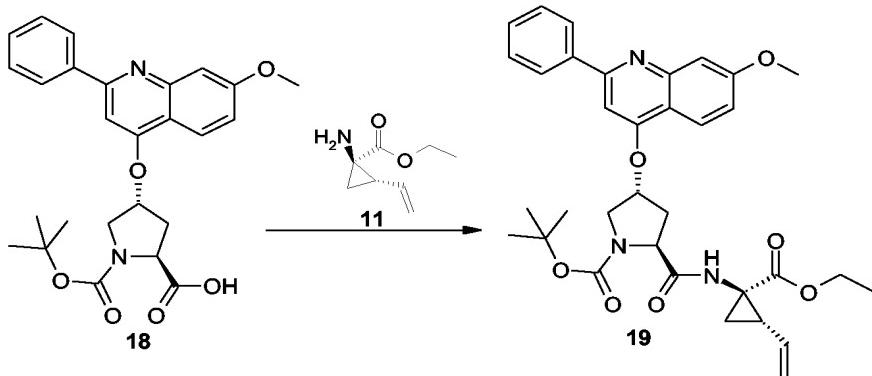
mmol) were added. The reaction mixture was heated at 50°C for 24h, then cooled down at room temperature and partitioned between water and CH₂Cl₂. The organic layers were dried (MgSO₄), filtered, and the solvent was evaporated. The crude material was purified by column chromatography on silica gel (CH₂Cl₂/EtOAc, 95:05) to give a solid which was successively triturated in water, filtered, dried, triturated in ether and dried again under high vacuum to give 23 mg (16%) of the title product **17** as a white powder: *m/z* = 530 (M+H)⁺; ¹H NMR (CDCl₃): 8.10 (d, *J* = 9.3 Hz, 1H), 7.50 (s, 1H); 7.39 (s, 1H); 7.25 (dd, *J* = 9.3 Hz, 2.5 Hz, 1H); 7.39-7.30 (bs, 1H); 5.90-5.83 (bs, 1H); 5.71 (dd, *J* = 8.0 Hz, 17.9 Hz, 1H); 5.18 (t, *J* = 10.1 Hz, 1H), 4.79 (dd, *J* = 7.3 Hz, 9.0 Hz, 1H), 4.1 (s, 3H), 4.09-3.97 (m, 1H), 3.81-3.66 (m, 2H), 3.62 (d, *J* = 11.6 Hz, 1H), 3.19-3.05 (m, 1H); 2.59-2.22 (m, 4H); 2.01-1.90 (m, 1H), 1.89 (dd, *J* = 5.8 Hz, 8.6 Hz, 1H), 1.70 (dd, *J* = 6.1 Hz, 9.8 Hz, 1H), 1.67-1.58 (m, 2H), 1.75-0.76 (m, 7H).

Example 4: Synthesis of 17-(7-methoxy-2-phenylquinolin-4-yloxy)-2,14-dioxo-3,15-diaza-13-oxatricyclo[13.3.0.0^{4,6}]octadec-7-ene-4-carboxylic acid (**22**)

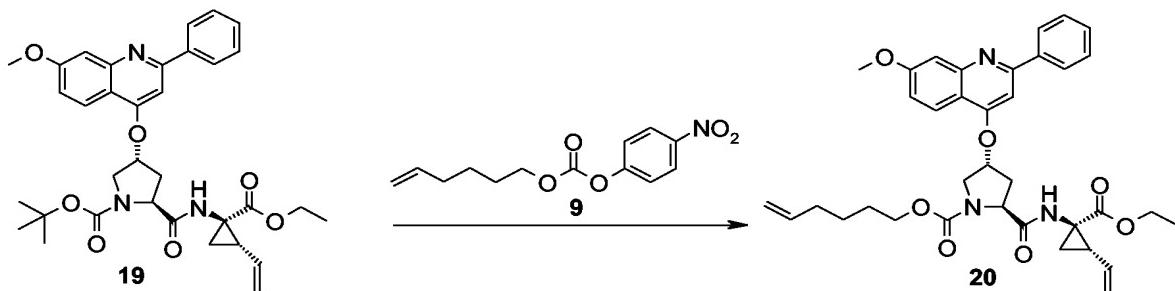
Step A



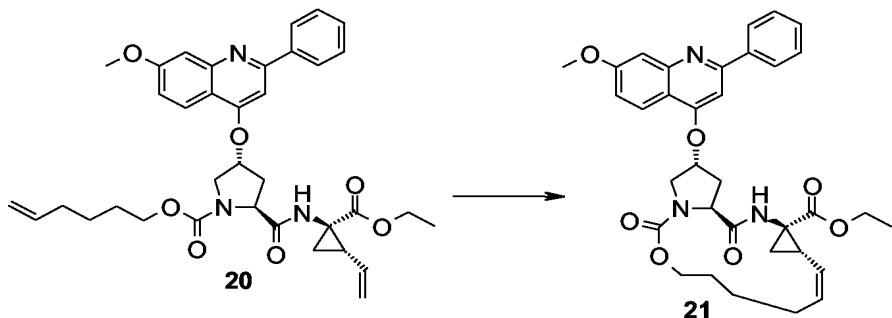
To a stirred solution of *N*-Boc-hydroxyproline (3.9 g, 16.9 mmol) in DMSO (90 mL) was added potassium *tert*-butoxide (4.5 g, 40.1 mmol). After 1 h, 4-chloro-2-phenyl-7-methoxy quinoline (4.5 g, 16.7 mmol) was added and the resulting solution was stirred at room temperature for 12 h. Then, the mixture was diluted with water (180 mL), washed with ethyl acetate (30 mL) and neutralized with 1N HCl. The solid was filtered, washed with water and dried to give 4.65g of the target product **18**. *m/z* = 464.2 (M+H)⁺.

Step B

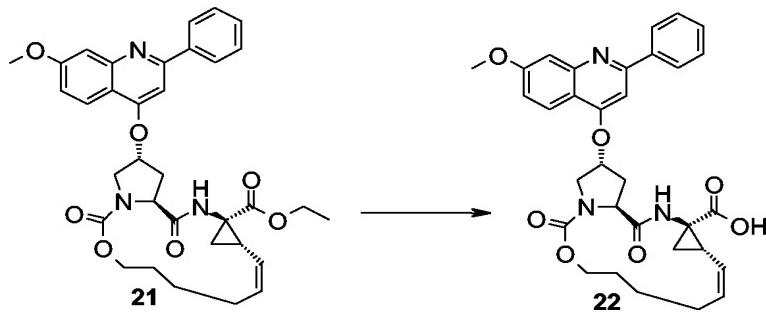
To a solution of 1-amino-2-vinylcyclopropanecarboxylic acid ethyl ester (**11**, 41 mg, 0.26 mmol), **18** (11 mg, 0.22 mmol), HATU (204 mg, 0.54 mmol) in DMF (4 mL) was added DIPEA (187 μ L, 1.08 mmol). After stirring at RT for 1 h, dichloromethane (4 mL) was added. The solution was successively washed with aqueous NaHCO₃ (sat) and with two portions of water. The organic layer was dried (Na₂SO₄) and concentrate to give the title product **19**: *m/z* = 602.2 (M+H)⁺.

Step C

To a solution of **19** (0.36 g, 0.60 mmol) in dichloromethane (5 mL) was added at 0°C trifluoroacetic acid in one portion. The reaction mixture was stirred at 0 °C for 30 min and additional 40 min at room temperature, then concentrated and concentrated from toluene (3 x 15 mL) to give an off-white foam. To this residue was added a solution of **9** (0.175 g, 0.66 mmol) in dichloromethane (10 mL) followed by diisopropylethylamine (0.32 mL, 1.8 mmol) and then refluxed for 48 h. The reaction mixture was then concentrated and re-dissolved in dichloromethane (15 mL) and diisopropylethylamine (0.32 ml, 1.8 mmol), then refluxed for another 48 h. The resulting light brown solution was then diluted with dichloromethane (15 mL), washed with aq. saturated sodium hydrogen carbonate (3 x 20 mL), dried (Na₂SO₄), filtered and evaporated. Purification by flash chromatography (gradient AcOEt/Hexanes 40:60 to 50:50) gave 240 mg (63%) of the desired product **20** as a colorless oil: *m/z* = 628 (M+H)⁺.

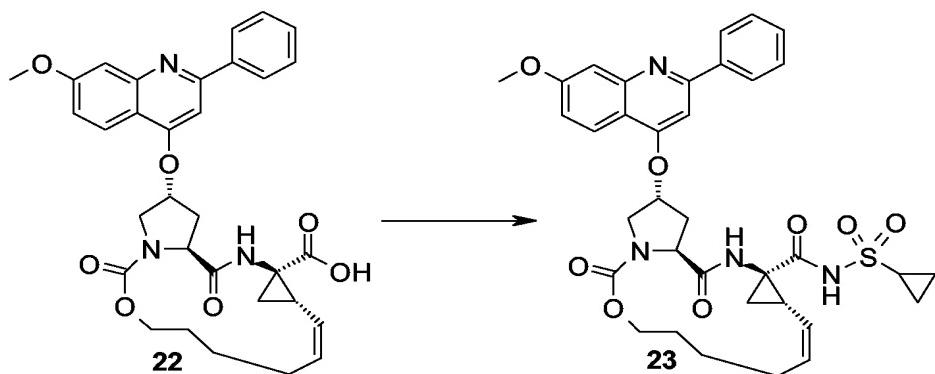
Step D

A solution of the di-alkene **20** (0.24 g, 0.38 mmol) in dichloroethane (240 mL) was successively degassed 3 times with nitrogen followed by once with argon, then Hoveyda-Grubbs 1st generation (0.016 g, 0.07 eq) was added and the reaction mixture was degassed twice more with argon, then refluxed under argon for 16 h. The reaction mixture was then allowed to cool down to room temperature, catalyst scavenger was added (0.13 g) and the resulting mixture was stirred for 1 h. The mixture was then filtered and evaporated. The residue was purified by flash chromatography (gradient AcOEt/Hexanes 40:60 to 50:50) to give 150 mg (67%) of the target product **21** as a colorless solid.

Step E

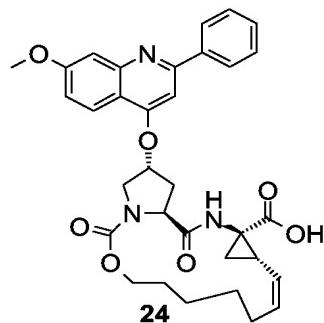
1M lithium hydroxide (3 mL) was added at room temperature to a solution of the ethyl ester **21** (0.15 g, 0.25 mmol) in 1:1 dioxane-methanol (6 mL). After 2h, methanol (1 mL) was added to the gel-like suspension, and the resulting solution was stirred for an additional 24 h. The reaction mixture was then acidified using acetic acid (0.5 mL), concentrated under reduced pressure. The residue was purified by flash chromatography (AcOEt/MeOH, 92:8 + 0.5 % of AcOH) to give 110 mg (76%) of the target compound **22** as a colorless solid: *m/z* = 572 (M+H)⁺.

Example 5: Synthesis of *N*-[17-(7-methoxy-2-phenylquinolin-4-yloxy)-2,14-dioxo-3,15-diaza-13-oxatricyclo[13.3.0.0^{4,6}]octadec-7-ene-4-carbonyl](cyclopropyl)sulfonamide (**23**)



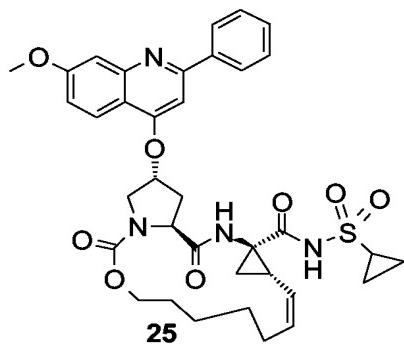
To a stirred suspension of the acid **22** (0.041 g, 0.072 mmol) in 3:1 dichloromethane-dimethylformamide (1.2 mL) was added *N*-ethyl-*N'*-(3-dimethylaminopropyl)-carbodiimide x HCl (0.027 g, 0.143 mmol) upon which a solution was obtained. The reaction mixture was stirred 10 min, after which 4-(dimethylamino)pyridine (0.009 g, 0.072 mmol) was added, and the reaction mixture was stirred another 40 min at room temperature. Then, a solution of the cyclopropylsulfonamide, prepared as described in WO03/053349, (0.035 g, 0.287 mmol) and 1,8-diazabicyclo[5.4.0]-undec-7-ene (0.043 ml, 0.287 mmol) was added and the tube was sealed and then put in the microwave at 100 °C for 40 minutes. The reaction mixture was then partitioned between ethyl acetate (20 mL), aq. 1 M hydrochloric acid and brine. The organic layer was pooled with the organic layer of another batch starting from 0.062 g, 0.108 mmol of the acid treated similar as above. The resulting solution was dried (Na_2SO_4), filtered and concentrated onto silica. The residue was purified by flash chromatography (gradient AcOEt:toluene 50:50 to 100:0 + 0.5 % AcOH followed by AcOEt/MeOH, 9:1). Appropriate fractions were concentrated and further purified on Preparative HPLC (Column: ACE 5 C8, 100 x 21.2 mm, ACE-122-1020) using flow = 15 mL/min, gradient 55% methanol/5 % acetonitrile in aq. 10 mM ammonium acetate to 90 % methanol in 10 min. Appropriate fractions were concentrated, re-dissolved in methanol, concentrated and lyophilized overnight to obtain an off-white solid. Finally this material was subjected to column chromatography (AcOEt/toluene, 1:1), to give 39 mg (32%) of the desired product **23** as a white powder: $m/z = 675 (\text{M}+\text{H})^+$. ^{13}C -NMR (125 MHz, CDCl_3): 6.4, 6.5, 22.8, 24.0, 25.3, 28.0, 31.3, 33.4, 37.4, 43.0, 53.8, 56.2, 58.2, 63.7, 76.1, 98.9, 108.3, 115.4, 118.8, 123.3, 126.0, 127.4, 128.0, 128.9, 129.3, 129.6, 130.3, 131.2, 139.8, 151.4, 154.5, 158.5, 160.5, 161.6, 169.9, 175.6.

Example 6: Synthesis of 18-(7-methoxy-2-phenylquinolin-4-yloxy)-2,15-dioxo-3,16-diaza-14-oxatricyclo[14.3.0.0^{4,6}]nonadec-7-ene-4-carboxylic acid (**24**)



The title compound **24** was synthesized from intermediate **19** and *O*-(hept-6-enyl)-*O*-(4-nitrophenyl) carbonate following the same procedure (steps C-E) described for the synthesis of 17-(7-methoxy-2-phenylquinolin-4-yloxy)-2,14-dioxo-3,15-diaza-13-oxatricyclo[13.3.0.0^{4,6}]octadec-7-ene-4-carboxylic acid (**22**): $m/z = 586$ ($M+H$)⁺.

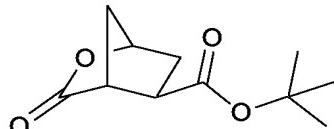
Example 7: Synthesis of *N*-[18-(7-methoxy-2-phenylquinolin-4-yloxy)-2,15-dioxo-3,16-diaza-14-oxatricyclo[14.3.0.0^{4,6}]nonadec-7-ene-4-carbonyl](cyclopropyl)sulfonamide (**25**)



The title compound **25** was synthesized from compound **24** following the same procedure described for the synthesis of *N*-[17-(7-methoxy-2-phenylquinolin-4-yloxy)-2,14-dioxo-3,15-diaza-13-oxatricyclo[13.3.0.0^{4,6}]octadec-7-ene-4-carbonyl]-cyclopropylsulfonamide (**23**): $m/z = 689$ ($M+H$)⁺.

Example 8:

Synthesis of 3-Oxo-2-oxa-bicyclo[2.2.1]heptane-5-carboxylic acid *tert*-butyl ester (**27**).

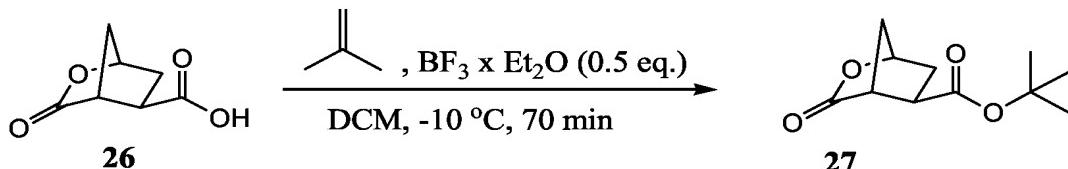


DMAP (14 mg, 0.115 mmol) and Boc_2O (252 mg, 1.44 mmol) was added to a stirred solution of **26** (180 mg, 1.15 mmol) in 2 mL CH_2Cl_2 under inert argon atmosphere at 0 °C. The reaction was allowed to warm to room temperature and was stirred overnight. The reaction mixture was concentrated and the crude product was purified by flash

column chromatography (toluene/ethyl acetate gradient 15:1, 9:1, 6:1, 4:1, 2:1), which gave the title compound (124 mg, 51%) as white crystals.

¹H-NMR (300 MHz, CD₃OD) δ 1.45 (s, 9H), 1.90 (d, *J*= 11.0 Hz, 1H), 2.10-2.19 (m, 3H), 2.76-2.83 (m, 1H), 3.10 (s, 1H), 4.99 (s, 1H); ¹³C-NMR (75.5 MHz, CD₃OD) δ 27.1, 33.0, 37.7, 40.8, 46.1, 81.1, 81.6, 172.0, 177.7.

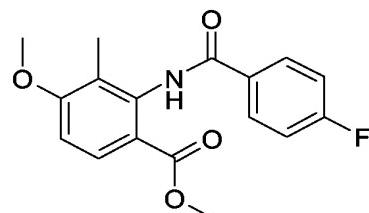
Alternative method for the preparation of compound 27



Compound **26** (13.9 g, 89 mmol) was dissolved in dichloromethane (200 ml) and then cooled to approximately -10°C under nitrogen. Isobutylene was then bubbled into the solution until the total volume had increased to approximately 250 ml which gave a “cloudy solution”. BF₃ × Et₂O (5.6 ml, 44.5 mmol, 0.5 eq.) was added and the reaction mixture was kept at approximately -10°C under nitrogen. After 10 min, a clear solution was obtained. The reaction was monitored by TLC (EtOAc-Toluene 3:2 acidified with a few drops of acetic acid and hexane-EtOAc 4:1, staining with basic permanganate solution). At 70 min only traces of compound **26** remained and aq. saturated NaHCO₃ (200 ml) was added to the reaction mixture, which was then stirred vigorously for 10 min. The organic layer was washed with saturated NaHCO₃ (3 x 200 ml) and brine (1 x 150 ml), then dried with sodium sulfite, filtered and concentrated into an oil containing small droplets. Upon addition of hexane to the residue the product crashed out. Addition of more hexane and heating to reflux gave a clear solution from which the product crystallized. The crystals were collected by filtration and was washed with hexane (rt), then air-dried for 72 h giving colourless needles (12.45 g, 58.7 mmol, 66% from first harvest)

Example 9: Synthesis of a quinazoline as a P2 building block

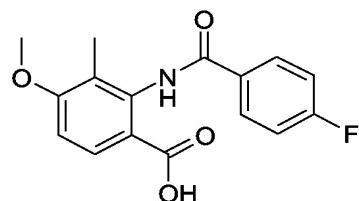
2-(4-Fluoro-benzoylamino)-4-methoxy-3-methyl-benzoic acid methyl ester (28)



4-Fluoro benzoic acid (700 mg, 5 mmol) was dissolved in dichloromethane (20 ml) and

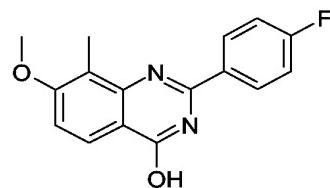
pyridine (2 ml). 2-Amino-4-methoxy-3-methyl-benzoic acid methyl ester (878 mg, 4.5 mmol) was added and the mixture was refluxed for 5 h. Water was added and the mixture was extracted with dichloromethane. The organic phase was dried, filtered and evaporated and the afforded residue was purified by column chromatography on silica gel, eluted with ether-pentane 1:1 which gave pure title compound (870 mg, 61 %). MS ($M+H^+$) 318.

2-(4-Fluoro-benzoylamino)-4-methoxy-3-methyl-benzoic acid (29)



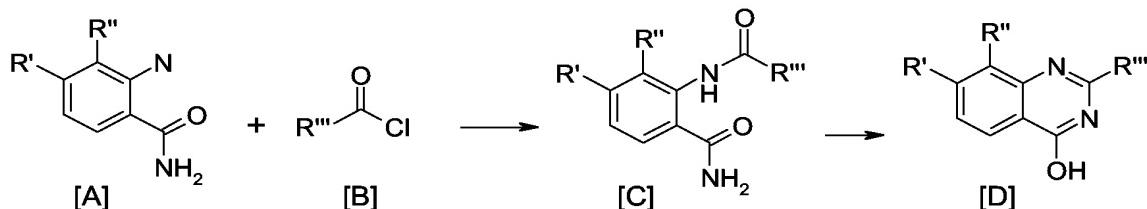
LiOH (1M, 4 mL) was added to a solution of 2-(4-fluoro-benzoylamino)-4-methoxy-3-methyl-benzoic acid methyl ester (28) (870 mg, 2.7 mmol), in tetrahydrofuran (15 ml), water (7.5 ml) and methanol (7.5 ml) . The mixture was heated to 50 °C for 4 h. Water (30 ml) was then added and the volume reduced to half. Acidification with acetic acid followed by filtration gave pure title compound (830 mg, 100 %).
MS ($M+H^+$) 304.

2-(4-Fluoro-phenyl)-7-methoxy-8-methyl-quinazolin-4-ol (30)



2-(4-Fluoro-benzoylamino)-4-methoxy-3-methyl-benzoic acid (29) (830 mg, 2.7 mmol) was heated to 150 °C in formamide (20 ml) for 4 h. The excess formamide was removed by distillation. Water was added and the precipitated product was filtered off to give pure title compound (642 mg, 83 %).

MS ($M+H^+$) 285.

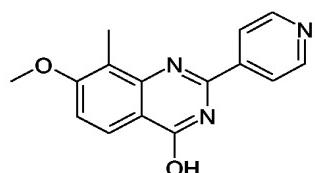
Example 10: General procedure for the preparation of substituted quinazolin-4-ols

To a suspension of a substituted 2-amino-benzamide [A] (1 eq) in dry THF (60 ml) was added pyridine (2 eq) and the mixture was cooled to 5 °C. The acid chloride [B] (1.25 eq) was added slowly and the mixture was stirred at room temperature overnight. The mixture was evaporated under reduced pressure and then suspended in water. The compound was left in the water for some hours, filtered and washed with cold water and diethyl ether. The product [C] was dried under vacuum. Yield: 90-100%. When the acid chloride [B] used was a nicotinyl chloride hydrochloride, then 2.5 eq of pyridine was used and the mixture was stirred for 2-3 days at room temperature instead of over night.

The formed amide [C] (1 eq) was added to a suspension of sodium carbonate (2.5 eq) in a 1:1 mixture of water and EtOH and the mixture was refluxed for two hours. The EtOH was removed under reduced pressure, a solution of 5% citric acid was added and the mixture was allowed to stay overnight. The product [D] was isolated by filtration, then washed with water and diethyl ether and dried under vacuum.

Example 11: 7-Methoxy-8-methyl-2-pyridin-3yl-quinazolin-4-ol (31)

The general procedure described in Example 10 was followed using 2-amino-4-methoxy-3-methyl benzamide as benzamide derivative and nicotinyl chloride hydrochloride as acid chloride, which gave the title compound (2.5g, 92%), $[M+H]=268$.

Example 12: 7-Methoxy-8-methyl-2-pyridin-4yl-quinazolin-4-ol (32)

The general procedure described in Example 10 was followed using 2-amino-4-methoxy-3-methyl benzamide as benzamide derivative and isonicotinoyl chloride hydrochloride as acid chloride, which gave the title compound (1.6 g, 60%), [M+H]=268.

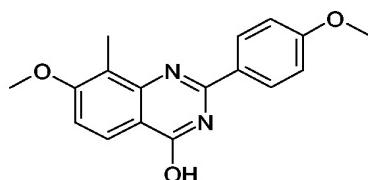
Example 13: 7-Methoxy-8-methyl-2-ethyl-quinazolin-4-ol (33)



The general procedure described in Example 10 was followed using 2-amino-4-methoxy-3-methyl benzamide as benzamide derivative [A] and acetic acid chloride as acid chloride [B], which gave the title compound (2.2 g, 100%).

¹H-NMR DMSO-D₆ δ 1.2 (m, 3H), 2.38 (s, 3H), 2.6 (m, 2H), 3.90 (s, 3H), 7.18 (d, 2H), 7.96 (d, 2H), 11.88 (s, 1H).

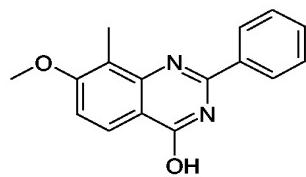
Example 14: 7-Methoxy-8-methyl-2-(4-methoxyphenyl)-quiazolin-4-ol (34)



The general procedure described in Example 10 was followed using 2-amino-4-methoxy-3-methyl benzamide as benzamide derivative [A] and 4-methoxybenzoic acid chloride as acid chloride [B], which gave the title compound (5.5 g, 92%).

¹H-NMR DMSO-D₆ δ 2.38 (s, 3H), 3.82 (s, 3H), 3.92 (s, 3H), 7.04 (d, 2H), 7.20 (d, 1H), 8.00 (d, 1H), 8.20 (d, 2H), 12.18 (s, 1H).

Example 15: 8-Methoxy-2-phenyl-quinazolin-4-ol (35)



The general procedure described in Example 10 was followed using 2-amino-4-methoxy-3-methyl benzamide as benzamide derivative [A] and benzoyl chloride as acid chloride [B], which gave the title compound (2.0 g, 80%), [M+H]=253.

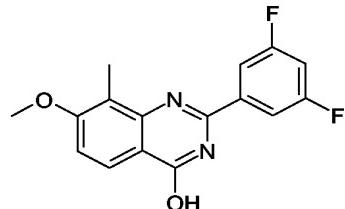
¹H-NMR DMSO-D₆ δ 3.97 (s, 3H), 7.39-7.72 (m, 6H), 8.19 (m, 2H), 12.48 (s, 1H).

Example 16: 2-(3-Fluoro-phenyl)-7-methoxy-8-methyl-quinazolin-4-ol (36)



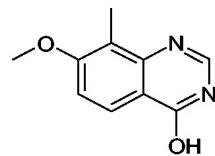
The general procedure described in Example 10 was followed using 2-amino-4-methoxy-3-methyl benzamide as benzamide derivative [A] and 3-fluoro-benzoyl chloride as acid chloride [B], which gave the title compound (2.1 g, 73%), [M+H]=271.

Example 17: 2-(3,5-Difluoro-phenyl)-7-methoxy-8-methyl-quinazolin-4-ol (37)



The general procedure described in Example 10 was followed using 2-amino-4-methoxy-3-methyl benzamide as benzamide derivative [A] and 3,5-difluoro-benzoyl chloride as acid chloride [B], which gave the title compound (2.1 g, 85%), [M+H]=303.

Example 18: 7-Methoxy-8-methyl-quinazolin-4-ol (38)



The title compound was formed as a biproduct when the ring closing reaction, step [B] to [C], in the general procedure was performed in DMF rather than in EtOH.

Example 19: Activity of compounds of formula (I)

Replicon assay

The compounds of formula (I) were examined for activity in the inhibition of HCV RNA replication in a cellular assay. The assay demonstrated that the compounds of formula (I) exhibited activity against HCV replicons functional in a cell culture. The cellular assay was based on a bicistronic expression construct, as described by Lohmann et al. (1999) Science vol. 285 pp. 110-113 with modifications described by

Krieger et al. (2001) Journal of Virology 75: 4614-4624, in a multi-target screening strategy. In essence, the method was as follows.

The assay utilized the stably transfected cell line Huh-7 luc/neo (hereafter referred to as Huh-Luc). This cell line harbors an RNA encoding a bicistronic expression construct comprising the wild type NS3-NS5B regions of HCV type 1b translated from an Internal Ribosome Entry Site (IRES) from encephalomyocarditis virus (EMCV), preceded by a reporter portion (FfL-luciferase), and a selectable marker portion (neo^R, neomycin phosphotransferase). The construct is bordered by 5' and 3' NTRs (non-translated regions) from HCV type 1b. Continued culture of the replicon cells in the presence of G418 (neo^R) is dependent on the replication of the HCV RNA. The stably transfected replicon cells that express HCV RNA, which replicates autonomously and to high levels, encoding *inter alia* luciferase, are used for screening the antiviral compounds.

The replicon cells were plated in 384 well plates in the presence of the test and control compounds which were added in various concentrations. Following an incubation of three days, HCV replication was measured by assaying luciferase activity (using standard luciferase assay substrates and reagents and a Perkin Elmer ViewLuxTm ultraHTS microplate imager). Replicon cells in the control cultures have high luciferase expression in the absence of any inhibitor. The inhibitory activity of the compound on luciferase activity was monitored on the Huh-Luc cells, enabling a dose-response curve for each test compound. EC50 values were then calculated, which value represents the amount of the compound required to decrease by 50% the level of detected luciferase activity, or more specifically, the ability of the genetically linked HCV replicon RNA to replicate.

Inhibition assay

The aim of this *in vitro* assay was to measure the inhibition of HCV NS3/4A protease complexes by the compounds of the present invention. This assay provides an indication of how effective compounds of the present invention would be in inhibiting HCV NS3/4A proteolytic activity.

The inhibition of full-length hepatitis C NS3 protease enzyme was measured essentially as described in Poliakov, 2002 Prot Expression & Purification 25 363 371. Briefly, the hydrolysis of a depsipeptide substrate, Ac-DED(Edans)EEAbu ψ [COO]ASK(Dabcyl)-NH₂ (AnaSpec, San José, USA), was measured spectrofluorometrically in the presence of a peptide cofactor, KKGSVVIVGRIVLSGK (Åke Engström, Department of Medical Biochemistry and Microbiology, Uppsala University, Sweden). [Landro, 1997 #Biochem 36 9340-9348]. The enzyme (1 nM) was incubated in 50 mM HEPES, pH

7.5, 10 mM DTT, 40% glycerol, 0.1% n-octyl-D-glucoside, with 25 μ M NS4A cofactor and inhibitor at 30 °C for 10 min, whereupon the reaction was initiated by addition of 0.5 μ M substrate. Inhibitors were dissolved in DMSO, sonicated for 30 sec. and vortexed. The solutions were stored at - 20°C between measurements.

The final concentration of DMSO in the assay sample was adjusted to 3.3%. The rate of hydrolysis was corrected for inner filter effects according to published procedures. [Liu, 1999 Analytical Biochemistry 267 331-335]. Ki values were estimated by non-linear regression analysis (GraFit, Erythacus Software, Staines, MX, UK), using a model for competitive inhibition and a fixed value for Km (0.15 μ M). A minimum of two replicates was performed for all measurements.

The following Table 1 lists compounds that were prepared according to any one of the above examples. The compounds are numbered with the same numbers provided in Examples 1-7. The activities of the compounds tested are also depicted.

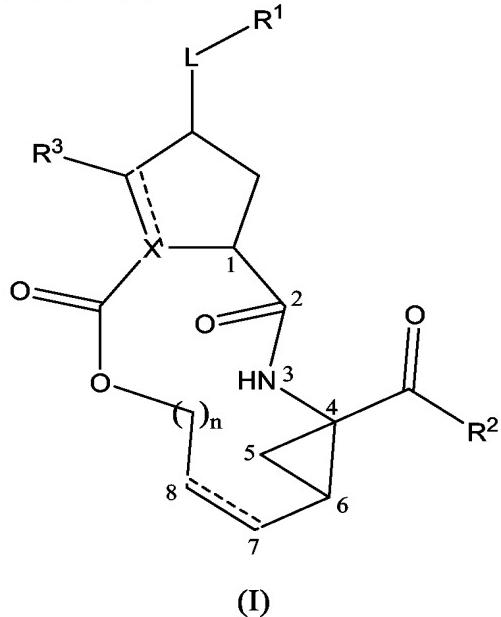
Table 1

Compound No.	Structural formula	EC ₅₀ Replicon assay (μ M)	Ki Enzymatic assay (nM)
23		1.082	0.2
22		>10	1070

Compound No.	Structural formula	EC ₅₀ Replicon assay (μM)	K _i Enzymatic assay (nM)
16		>10	1000
17		>10	43
24		>10	40
25		0.481	2.4

Claims

1. A compound having the formula



the *N*-oxides, addition salts, and stereochemically isomeric forms thereof, wherein each dashed line (represented by - - - -) represents an optional double bond; **X** is N, CH and where X bears a double bond it is C;

R¹ is aryl or a saturated, a partially unsaturated or completely unsaturated 5 or 6 membered monocyclic or 9 to 12 membered bicyclic heterocyclic ring system wherein said ring system contains one nitrogen, and optionally one to three additional heteroatoms selected from the group consisting of oxygen, sulfur and nitrogen, and wherein the remaining ring members are carbon atoms; wherein said ring system may be optionally substituted on any carbon or nitrogen ring atom with one, two, three, or four substituents each independently selected from C₃₋₇cycloalkyl, aryl, Het, -C(=O)-NR^{4a}R^{4b}, -C(=O)R⁶, -C(=O)OR^{5a}, and C₁₋₆alkyl optionally substituted with C₃₋₇cycloalkyl, aryl, Het, -C(=O)NR^{4a}R^{4b}, -NR^{4a}R^{4b}, -C(=O)R⁶, -NR^{4a}C(=O)R⁶, -NR^{4a}SO_pR⁷, -SO_pR⁷, -SO_pNR^{4a}R^{4b}, -C(=O)OR⁵, or -NR^{4a}C(=O)OR^{5a}; and wherein the substituents on any carbon atom of the heterocyclic ring may also be selected from -OR⁸, -SR⁸, halo, polyhalo-C₁₋₆alkyl, oxo, thio, cyano, nitro, azido, -NR^{4a}R^{4b}, -NR^{4a}C(=O)R⁶, -NR^{4a}SO_pR⁷, -SO_pR⁷, -SO_pNR^{4a}R^{4b}, -C(=O)OH, and -NR^{4a}C(=O)OR^{5a};

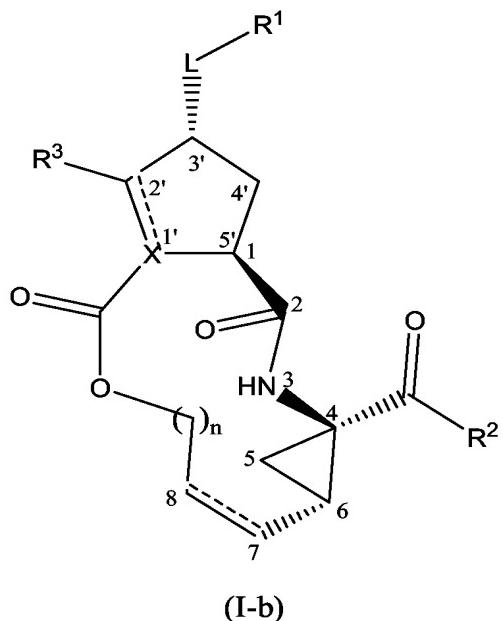
L is a direct bond, -O-, -O-C₁₋₄alkanediyl-, -O-C(=O)-, -O-C(=O)-NR^{4a}- or -O-C(=O)-NR^{4a}C₁₋₄alkanediyl-;

R² represents hydrogen, -OR⁵, -C(=O)OR⁵, -C(=O)R⁶, -C(=O)NR^{4a}R^{4b}, -C(=O)NHR^{4c}, -NR^{4a}R^{4b}, -NHR^{4c}, -NR^{4a}SO_pNR^{4a}R^{4b}, -NR^{4a}SO_pR⁷, or B(OR⁵)₂;

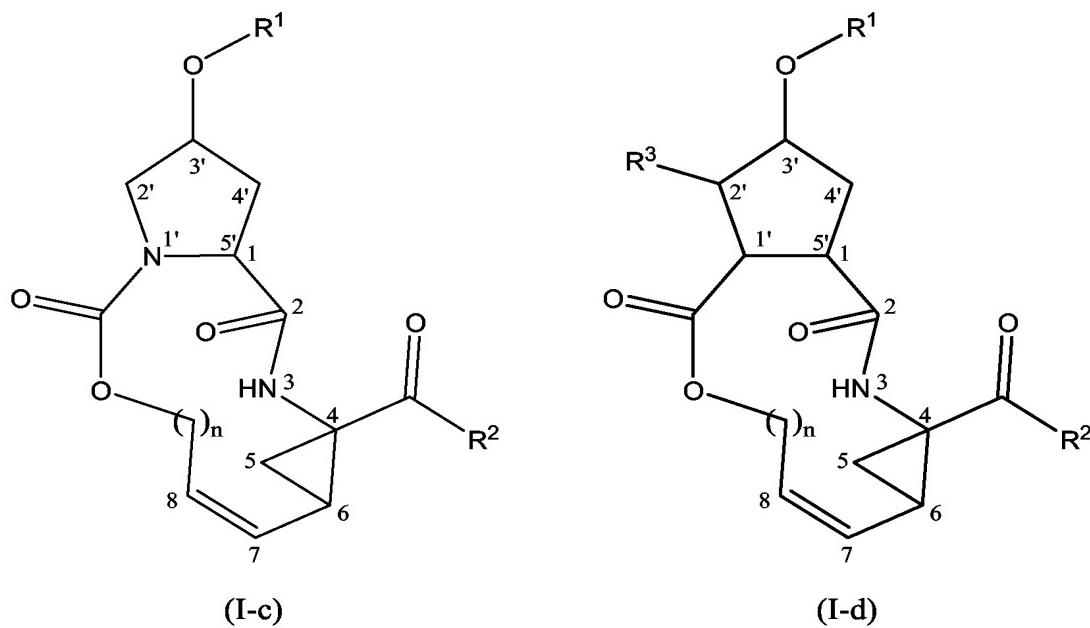
R³ is hydrogen, and where **X** is C or CH, **R³** may also be C₁₋₆alkyl;
n is 3, 4, 5, or 6;
p is 1 or 2;
each **R^{4a}** and **R^{4b}** are, independently, hydrogen, C₃₋₇cycloalkyl, aryl, Het, C₁₋₆alkyl
optionally substituted with halo, C₁₋₄alkoxy, cyano, polyhaloC₁₋₄alkoxy,
C₃₋₇cycloalkyl, aryl, or with Het; or **R^{4a}** and **R^{4b}** taken together with the nitrogen
atom to which they are attached form pyrrolidinyl, piperidinyl, piperazinyl,
4-C₁₋₆alkylpiperazinyl, 4-C₁₋₆alkylcarbonyl-piperazinyl, and morpholinyl; wherein
the morpholinyl and piperidinyl groups may be optionally substituted with one or
with two C₁₋₆alkyl radicals;
R^{4c} is C₃₋₇cycloalkyl, aryl, Het, -O-C₃₋₇cycloalkyl, -O-aryl, -O-Het, C₁₋₆alkyl, or
C₁₋₆alkoxy, wherein said C₁₋₆alkyl, or C₁₋₆alkoxy may be each optionally
substituted with -C(=O)OR⁵, C₃₋₇cycloalkyl, aryl, or Het;
R⁵ is hydrogen; C₂₋₆alkenyl; Het; C₃₋₇cycloalkyl optionally substituted with C₁₋₆alkyl;
or C₁₋₆alkyl optionally substituted with C₃₋₇cycloalkyl, aryl or Het;
R^{5a} is C₂₋₆alkenyl, C₃₋₇cycloalkyl, Het, or C₁₋₆alkyl optionally substituted with
C₃₋₇cycloalkyl, aryl or Het;
R⁶ is hydrogen, C₁₋₆alkyl, C₃₋₇cycloalkyl, or aryl;
R⁷ is hydrogen; polyhaloC₁₋₆alkyl; aryl; Het; C₃₋₇cycloalkyl optionally substituted with
C₁₋₆alkyl; or C₁₋₆alkyl optionally substituted with C₃₋₇cycloalkyl, aryl or Het;
aryl as a group or part of a group is phenyl, naphthyl, indanyl, or 1,2,3,4-tetrahydro-
naphthyl, each of which may be optionally substituted with one, two or three
substituents selected from halo, C₁₋₆alkyl, polyhaloC₁₋₆alkyl, hydroxy,
C₁₋₆alkoxy, polyhaloC₁₋₆alkoxy, C₁₋₆alkoxyC₁₋₆alkyl, carboxyl, C₁₋₆alkylcarbonyl,
C₁₋₆alkoxycarbonyl, cyano, nitro, amino, mono- or diC₁₋₆alkylamino, amino-
carbonyl, mono- or diC₁₋₆alkylaminocarbonyl, azido, mercapto, C₃₋₇cycloalkyl,
phenyl, pyridyl, thiazolyl, pyrazolyl, pyrrolidinyl, piperidinyl, piperazinyl,
4-C₁₋₆alkylpiperazinyl, 4-C₁₋₆alkylcarbonyl-piperazinyl, and morpholinyl; wherein
the morpholinyl and piperidinyl groups may be optionally substituted with one or
with two C₁₋₆alkyl radicals; and the phenyl, pyridyl, thiazolyl, pyrazolyl groups
may be optionally substituted with 1, 2 or 3 substituents each independently
selected from C₁₋₆alkyl, C₁₋₆alkoxy, halo, amino, mono- or diC₁₋₆alkylamino;
Het as a group or part of a group is a 5 or 6 membered saturated, partially unsaturated
or completely unsaturated heterocyclic ring containing 1 to 4 heteroatoms each
independently selected from nitrogen, oxygen and sulfur, said heterocyclic ring
being optionally condensed with a benzene ring, and wherein the group Het as a
whole may be optionally substituted with one, two or three substituents each
independently selected from the group consisting of halo, C₁₋₆alkyl, polyhalo-

C_{1-6} alkyl, hydroxy, C_{1-6} alkoxy, polyhalo C_{1-6} alkoxy, C_{1-6} alkoxy C_{1-6} alkyl, carboxyl, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, cyano, nitro, amino, mono- or di C_{1-6} alkyl-amino, aminocarbonyl, mono- or di C_{1-6} alkylaminocarbonyl, C_{3-7} cycloalkyl, phenyl, pyridyl, thiazolyl, pyrazolyl, pyrrolidinyl, piperidinyl, piperazinyl, 4- C_{1-6} alkylpiperazinyl, 4- C_{1-6} alkylcarbonyl-piperazinyl, and morpholinyl; wherein the morpholinyl and piperidinyl groups may be optionally substituted with one or with two C_{1-6} alkyl radicals; and the phenyl, pyridyl, thiazolyl, pyrazolyl groups may be optionally substituted with 1, 2 or 3 substituents each independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, halo, amino, mono- or di C_{1-6} alkylamino.

2. A compound according to claim 1 wherein the compound has the formula (I-b):

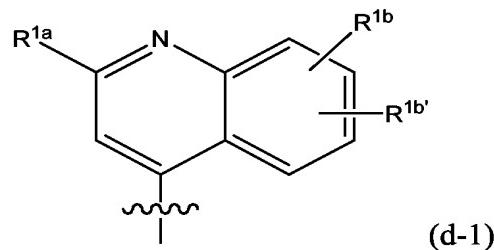


3. A compound according to any one of claims 1-2, wherein the compound has the formula (I-c) or (I-d):

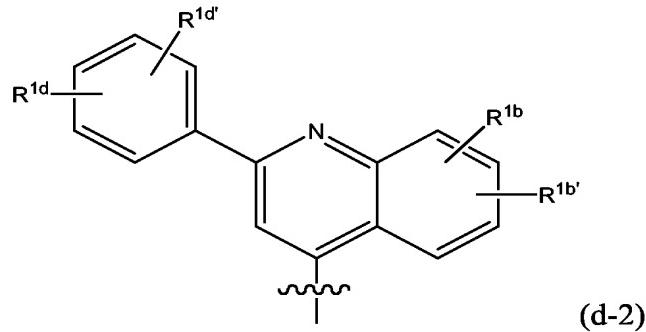


4. A compound according to any one of claims 1-2, wherein L is $-\text{O}-$, $-\text{O-CO-}$ or a direct bond.

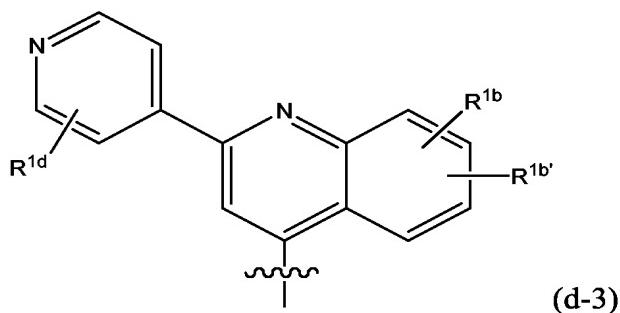
5. A compound according to claims 3 or 4 wherein L is $-\text{O}-$ and R^1 is
(d-1) a radical of formula



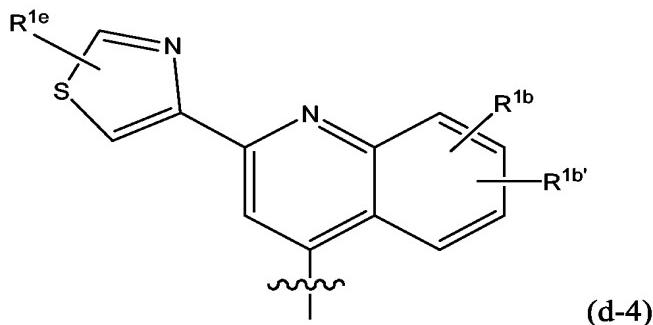
(d-2) a radical of formula



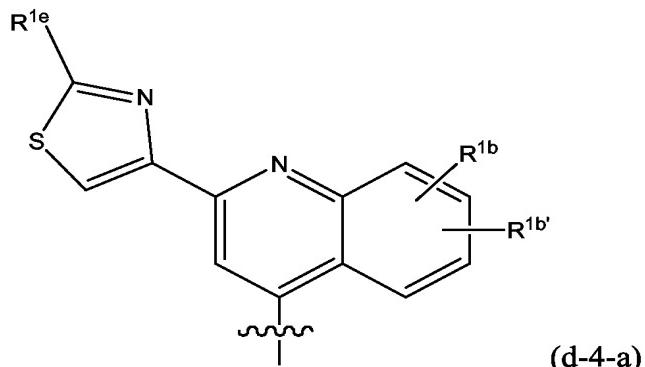
(d-3) a radical of formula



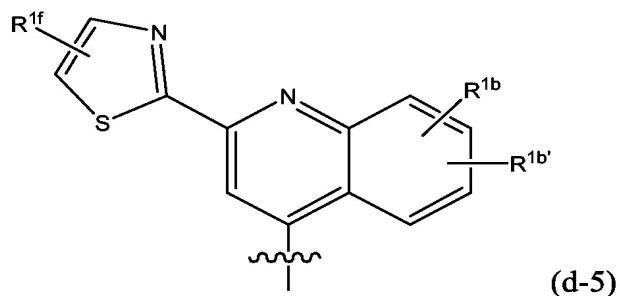
(d-4) a radical of formula



or in particular, (d-4-a) a radical of formula

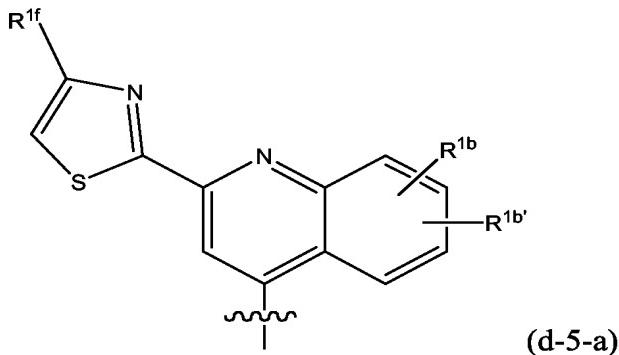


(d-5) a radical of formula



wherein in radicals (d-1) – (d-5), as well as in (d-4-a) and (d-5-a):
 each R^{1a} , R^{1b} , $R^{1b'}$, R^{1d} , $R^{1d'}$, R^{1e} , R^{1f} are independently any of the substituents selected from those mentioned as possible substituents on the monocyclic or bicyclic ring systems of R^1 , as specified in claim 1.

6. A compound according to claim 3 or 4 wherein L is $-O-$ and R¹ is a radical of formula



wherein R^{1f} is hydrogen, C₁₋₆alkyl, amino, mono- or diC₁₋₆alkylamino, pyrrolidinyl, piperidinyl, piperazinyl, 4- C₁₋₆alkylpiperazinyl (in particular 4-methylpiperazinyl), or morpholinyl.

7. A compound according to any one of claims 1-6, wherein

- (f) R² is $-NHR^{4c}$, where R^{4c} is C₁₋₆alkyl, aryl, Het, C₁₋₆alkoxy, -O-aryl, or $-O-Het$; or
- (g) R² is $-OR^5$, where R⁵ is methyl, ethyl, *tert*-butyl, or hydrogen; or
- (h) R² is $-NHS(=O)_2R^7$, where R⁷ is methyl, cyclopropyl, methylcyclopropyl, or phenyl; or
- (i) R² is $-C(=O)OR^5$, $-C(=O)R^6$, $-C(=O)NR^{4a}R^{4b}$, or $-C(=O)NHR^{4c}$, wherein R^{4a}, R^{4b}, R^{4c}, R⁵, or R⁶ are as defined are as defined in any one of claims 1-4, and where R^{4c} is cyclopropyl; or
- (j) R² is $-NHS(=O)_2NR^{4a}R^{4b}$ where R^{4a} and R^{4b} are, each independently, hydrogen, C₃₋₇cycloalkyl or C₁₋₆alkyl.

8. A compound according to any one of claims 1-7 wherein n is 4 or 5.

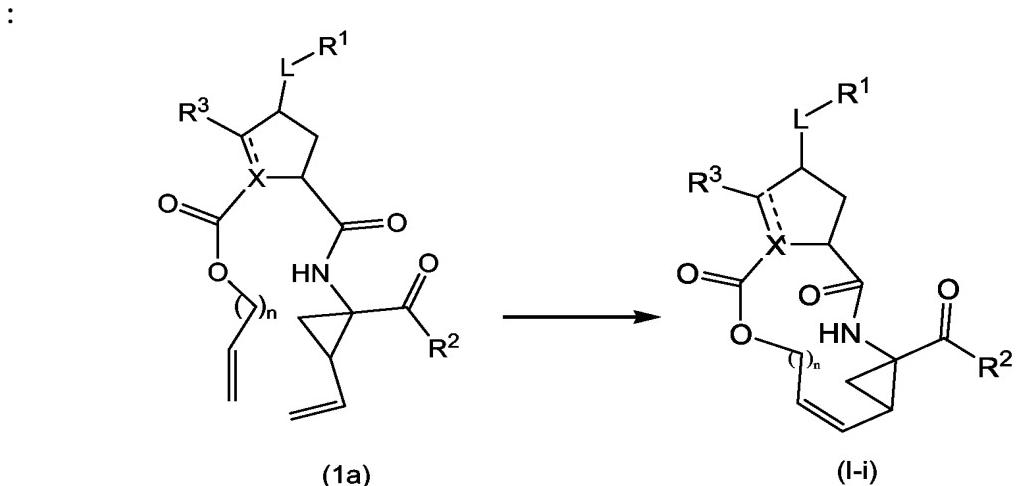
9. A compound according to any one of claims 1-8 wherein X is N.

10. A compound according to any one of claims 1-8 wherein X is CH and the bond between X and the carbon atom bearing R³ is a single bond.

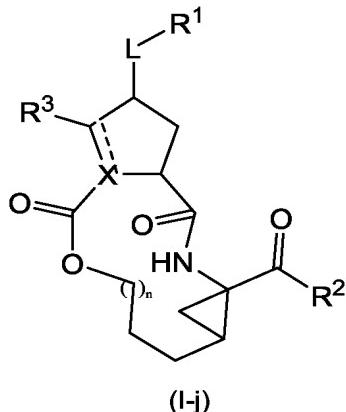
11. A compound according to any one of claims 1-9 wherein R³ is hydrogen.

12. A compound according to any of claims 1-11 other than an N-oxide, or salt.

13. A combination comprising
 - (a) a compound as defined in any one of claims 1 to 12 or a pharmaceutically acceptable salt thereof; and
 - (b) ritonavir, or a pharmaceutically acceptable salt thereof.
 14. A pharmaceutical composition comprising a carrier, and as active ingredient an anti-virally effective amount of a compound as claimed in any one of claims 1-12 or a combination according to claim 13.
 15. A compound according to any of claims 1-12 or a combination according to claim 13, for use as a medicament.
 16. Use of a compound according to any of claims 1-12 or a combination according to claim 13, for the manufacture of a medicament for inhibiting HCV replication.
 17. A method of inhibiting HCV replication in a warm-blooded animal said method comprising the administration of an effective amount of a compound according to any of claims 1-12 or an effective amount of each component of the combination according to claim 13.
 18. A process for preparing a compound as claimed in any of claims 1 - 12, wherein said process comprises:
 - (a) preparing a compound of formula (I) wherein the bond between C₇ and C₈ is a double bond, which is a compound of formula (I-i), by forming a double bond between C₇ and C₈, in particular via an olefin metathesis reaction, with concomitant cyclization to the macrocycle as outlined in the following reaction scheme:

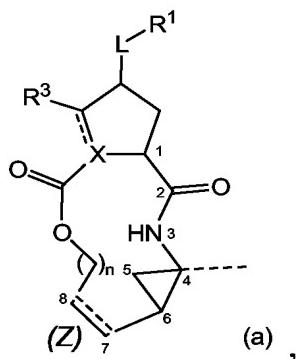


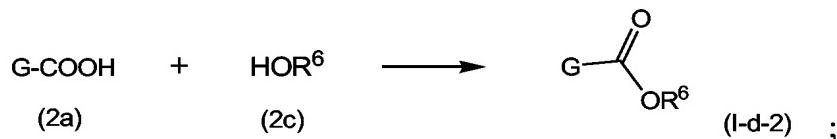
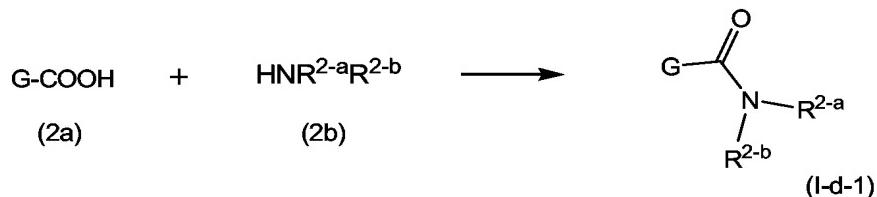
(b) converting a compound of formula (I-d) to a compound of formula (I) wherein the link between C7 and C8 in the macrocycle is a single bond, i.e. a compound of formula (I-j):



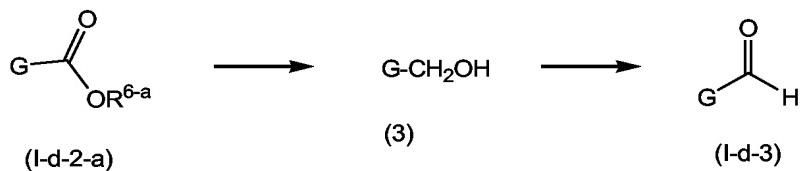
by a reduction of the C7-C8 double bond in the compound of formula (I-i);

(c) preparing a compound of formula (I) wherein R² represents -NR^{5a}R^{5b}, -NHR^{5c}, -NHSO_pNR^{5a}R^{5b}, -NR^{5a}SO_pR⁸, these groups being collectively represented by -NR^{2-a}R^{2-b}, said compound being represented by formula (I-d-1), by forming an amide bond between an intermediate (III) and an amine H-NR^{2-a}R^{2-b} (IV-a), or preparing a compound of formula (I) wherein R² represents -OR⁶, i.e. a compound (I-d-2), by forming an ester bond between an intermediate (III) and an alcohol (IV-b) as outlined in the following scheme wherein G represents a group:

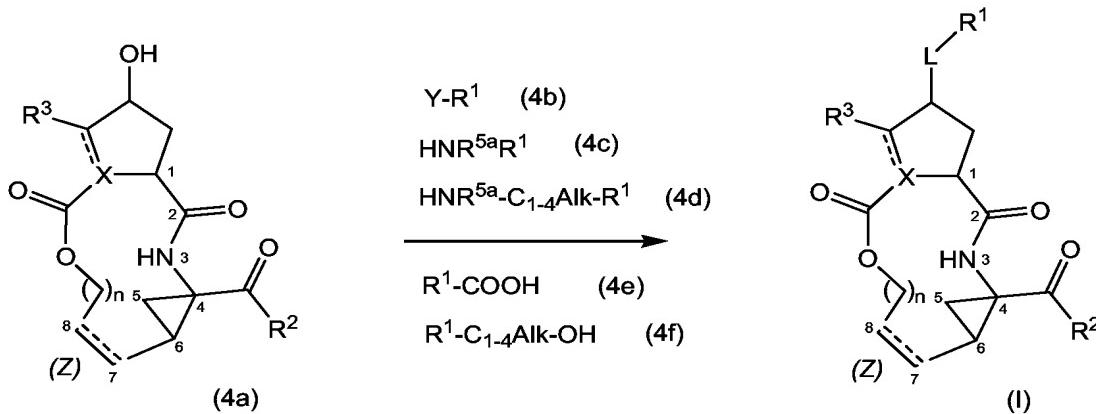




(d) preparing a compound of formula (I) wherein R² represents hydrogen, i.e. a compound (I-d-3), from an ester (I-d-2-a), which is an intermediate of formula (I-d-2) wherein R⁶ is C₁₋₄alkyl, by a reduction reaction to a corresponding alcohol (I-d-3), followed by an oxidation reaction with a mild oxidant:



(e) reacting an intermediate (V) with intermediates (4b), (4c), (4d), (4e) or (4f) as outlined in the following reaction scheme wherein the various radicals have the meanings specified above and C₁₋₄Alk represents C₁₋₄alkanediyl:



and wherein Y in (4b) represents hydroxy or a leaving group; which reaction in particular is an O-arylation reaction where Y represents a leaving group, or a Mitsunobu reaction, where Y is hydroxy;

(f) preparing a compound of formula (I) wherein L is a urethane group (L is -O-C(=O)-NR^{5a}-) by reacting an intermediate (4a) with an amine (4c) or (4d) in the presence of a carbonyl introducing agent, the latter in particular comprising phosgene or a phosgene derivative;

- (g) preparing compounds of formula (I) wherein L is $-O-C(=O)-$ by reacting an alcohol (4a) with an acid (4e) or active derivative thereof, such as a corresponding acylating agent, in particular an acid anhydride or acid halide;
- (h) preparing compounds of formula (I) wherein L is $-O-C_{1-4}alkanediyl-$ by an ether forming reaction between (4a) and (4f);
- (i) converting compounds of formula (I) into each other by a functional group transformation reaction; or
- (j) preparing a salt form by reacting the free form of a compound of formula (I) with an acid or a base.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/064814

A. CLASSIFICATION OF SUBJECT MATTER	INV.	C07D487/04	C07K5/078	A61K38/05	A61K31/33	A61P31/14
		C07D413/12				

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D C07K A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00/59929 A (BOEHRINGER INGELHEIM LTD; TSANTRIZOS, YOULA, S; CAMERON, DALE, R; FAU) 12 October 2000 (2000-10-12) cited in the application claim 1	1-18
A	WO 2005/010029 A (ENANTA PHARMACEUTICALS, INC; WU, FRANK, X., H; NAKAJIMA, SUANNE; OR, Y) 3 February 2005 (2005-02-03) claim 1	1-18



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority, claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 October 2006	12/10/2006
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer De Jong, Bart

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2006/064814

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 17 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2006/064814

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